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REVIEW OF THE SCIENTIFIC BASIS OF THE ENVIRONMENTAL PROTECTION AGENCY'S CARCINOGENIC RISK ASSESSMENT ON FORMALDEHYDE

REPORT

BY THE

COMMITTEE ON SCIENCE AND TECHNOLOGY

together with

ADDITIONAL AND MINORITY VIEWS

MAY 24, 1983.—Committed to the Committee of the Whole House on the State of the Union and ordered to be printed

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LETTER OF SUBMITTAL

U.S. HOUSE OF REPRESENTATIVES,
Washington, D.C., May 24, 1983.

Hon. THOMAS P. O'NEILL, Jr.,
The Speaker, U.S. House of Representatives, Washington, D.C.

DEAR MR. SPEAKER: By direction of the Committee on Science and Technology, I submit herewith the Committee's report to the 98th Congress. The Committee's report is based on an investigative study made by its Investigations and Oversight Subcommittee.

DON FUQUA, *Chairman.*

Enclosure.

LETTER OF TRANSMITTAL

HOUSE OF REPRESENTATIVES,
COMMITTEE ON SCIENCE AND TECHNOLOGY,
Washington, D.C., May 24, 1983.

Hon. DON FUQUA,
Chairman, Committee on Science and Technology,
U.S. House of Representatives.

DEAR MR. CHAIRMAN: I am pleased to transmit a report of the Subcommittee on Investigations and Oversight's review of the Environmental Protection Agency's carcinogenic risk assessment of formaldehyde. The report is the result of an extensive review by the Subcommittee and of its hearing on this issue held on May 20, 1982.

Generally, the Subcommittee concluded that the process used by EPA to gather and analyze data on formaldehyde was scientifically questionable and gave the appearance of bias. The Subcommittee found that non-peer review analysis and data were used by EPA to arrive at its decision, rigorous staff analysis of data was ignored or changed and the scientific support for the EPA decision was not scientifically reviewed. More fundamentally and more troubling was the fact that in reaching its decision, EPA departed from traditional and well accepted principles for carcinogenic risk assessment without valid scientific basis and without opportunity for scientific peer review or public comment. In sum the process and procedure used by EPA in arriving at its decision not to regulate formaldehyde did nothing to enhance the credibility of the agency generally, and tends to undermine the scientific integrity of EPA.

In light of the Subcommittee's findings, we intend to continue our oversight of EPA's further evaluation of formaldehyde. Additionally, and more importantly, the Subcommittee intends to continue its review of EPA's procedures for carcinogenic risk assessment and to include within such review other executive branch agency interpretations of the scientific basis for carcinogenic risk assessment.

The Subcommittee report contains two recommendations.

(1) That traditional principles for carcinogenic risk assessment be followed by EPA until such time as they are caused to be modified by new scientific findings, and then only after a reasonable opportunity for peer and public review.

(2) That the scientific basis of EPA decisions not to regulate a substance, because such decisions can have as great an impact on the public health as decisions to regulate can have on the affected industry, be subject to adequate and impartial scientific review within, and where appropriate, outside the agency.

The enclosed report summarizes the issues and viewpoints offered at the hearing and contains the findings and recommendations of the Subcommittee.

Finally, I would like to express my appreciation to Michael Simpson, Analyst in the Science Policy Research Division of the Congressional Research Service for his assistance in helping the Subcommittee in the preparation of this report.

Sincerely,

ALBERT GORE, JR.,
Chairman, Subcommittee on Investigations and Oversight.

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98TH CONGRESS } HOUSE OF REPRESENTATIVES { REPORT
1st Session } { No. 98–216

REVIEW OF THE SCIENTIFIC BASIS OF THE ENVIRONMENTAL PROTECTION AGENCY'S CARCINOGENIC RISK ASSESSMENT ON FORMALDEHYDE

MAY 24, 1983.—Committed to the Committee of the Whole House on the State of the Union and ordered to be printed

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Mr. FUQUA, from the Committee on Science and Technology, submitted the following

REPORT

together with

ADDITIONAL AND MINORITY VIEWS

[Based on an investigative study by the Investigations and Oversight Subcommittee]

On October 6, 1981, the Committee on Science and Technology approved and adopted a report entitled "Review of the Scientific Basis of the Environmental Protection Agency's Carcinogenic Risk Assessment on Formaldehyde." The Chairman was directed to transmit a copy to the Speaker of the House.

REVIEW OF THE SCIENTIFIC BASIS
OF THE ENVIRONMENTAL PROTECTION AGENCY'S
CARCINOGENIC RISK ASSESSMENT ON FORMALDEHYDE

Introduction

On February 10, 1982, John Todhunter, Assistant Administrator for Pesticides and Toxic Substances at the U.S. Environmental Protection Agency, transmitted his recommendation on formaldehyde to the EPA Administrator, Anne Gorsuch. Dr. Todhunter recommended the EPA not consider formaldehyde a priority chemical for action under section 4(f) of the Toxic Substances Control Act [15 U.S.C. § 2603(f)][1]

Because of the ubiquity of formaldehyde -- it is used in hundreds of products from plyboard and cosmetics to home insulation -- and because the U.S. Consumer Product Safety Commission (CPSC) was considering banning urea-formaldehyde foam (UFFI) in home insulation,[2]

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1 Section 4(f), entitled "Required Action," provides: Upon the receipt of (1) any test data required to be submitted this Act, or (2) any other information available to the Administrator, which indicates to the Administrator that there may be a reasonable basis to conclude that a chemical substance or mixture presents or will present a significant risk of serious or widespread harm to human beings from cancer, gene mutuations, or birth defects, the Administrator shall, within the 180 day period beginning on the date of the receipt of such data or information, initiate appropriate action under §§5, 6, or 7 to prevent or reduce to a sufficient extent such risk or publish in the Federal Register a finding that such risk is not unreasonable. For good cause shown the Administrator may extend such period for an additional period of not more than 90 days. The Administrator shall publish in the Federal Register notice of any such extension and the reasons therefor. 15 U.S.C. §2603(f).

2 On February 22, 1982, CPSC issued a regulation banning
(Footnote continued)

Dr. Todhunter's decision was eagerly awaited and bound to be controversial.

The public controversy over EPA's decision focused on the question of whether formaldehyde presented an "unreasonable" cancer risk to humans, and, therefore, whether EPA should have acted expeditiously -- as the CPSC had done -- to control exposures to formaldehyde.

Major concerns were strongly expressed in the scientific community as well, concerns about the integrity of the scientific process at EPA and about the scientific rationale for EPA's decision, which had been clearly articulated in the Todhunter memorandum of February 10.[3]

In the ensuing public and scientific debate, allegations were made concerning biased interpretation of scientific data, biased procedures used for data collection, and attempts to intimidate and otherwise put undue influence on agency scientists to force changes in scientific

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[2](continued)
the use of UFFI in home insulation because of its non-carcinogenic and carcinogenic health risk. 47 F.R. 14366 (April 2, 1982).

[3] See generally this report, and Hearings before the Subcommittee on Investigations and Oversight, Committee on Science and Technology, U. S. House of Representatives, "Formaldehyde: Review of Scientific Basis of EPA's Carcinogenic Risk Assessment", held May 20, 1982 (hereinafter "Hearing Record"), letters of Dr. Upton at Appendix 7, and Dr. Weinhouse at p. 11.

evaluations. Fundamental questions were asked about whether the EPA decision had effectively, without public or scientific peer review, rewritten the longstanding and almost universally accepted scientific rules used by agencies to assess whether exposure to a chemical substance has the potential to cause cancer in humans. Stated simply, had EPA unilaterally changed the rules of the game?

The Subcommittee decided to review EPA's decision not to designate formaldehyde a 4(f) chemical because of these allegations, made by well-respected scientists, which if true, would raise serious concerns about the performance of an agency charged with protecting the public health.

The Subcommittee also undertook its review of the EPA decision because of the precedent it might set, not only for EPA but for other executive branch agencies as well, since the decision was the first major assessment of a potential carcinogen by the new Administration. The Subcommittee's review also appears timely since EPA had developed a thorough record to support its decision, including an explanation of the decision by Dr. Todhunter,[4] and the public record had matured to a point where the process and procedures used by EPA could be meaningfully evaluated.

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4 Memorandum of Dr. John Todhunter, February 10, 1982. See Appendix B.

This report contains the findings, conclusions and recommendations from the Subcommittee's extensive investigation and its hearing on this matter held on May 20, 1982.

BACKGROUND

A. Issues Considered by the Subcommittee

Generally the Subcommittee considered three questions:

1. Did EPA depart from the traditional and widely supported principles for carcinogenic risk assessment in its formaldehyde decision? If so, has EPA articulated valid scientific reasons for departing from well-established principles?

2. Were the procedures used by EPA to obtain and interpret scientific data and to review the scientific basis of its decision undertaken in a manner so as to preserve the integrity of the scientific process at EPA and enhance the credibility of its decision?

3. Does the EPA decision document (Todhunter Memorandum) present a balanced and scientifically defensible interpretation of the data on the carcinogenicity potential of formaldehyde?

B. Identification of Carcinogens: Principles for Carcinogenic Risk Assessment

Central to the Subcommittee's inquiry is the question of whether EPA departed from traditionally accepted principles for carcinogenic risk assessment. The discussion that follows is intended to provide background on those principles. Briefly stated the principles are as follows:

o Properly designed and well-conducted tests using appropriate animal species are accepted as a valid way to identify chemical substances that may cause cancer in humans.

o Positive human data (epidemiology) are not necessary to regard an agent as a potential human carcinogen.

o It is not now possible to extrapolate from animal data to a "safe" population threshold for any carcinogen regardless of the mechanism of action.

The purpose of this section is to provide background on the scientific methods for identification of carcinogens, interpretation of test results, and extrapolation of animal data to humans for predicting risk. Some controversy exists surrounding many aspects of the identification and regulation of carcinogens, and the simplified discussion that follows is bound to be contain generalities that some may object to. However, the discussion is included here to give the reader

some general frame of reference. The references in the appendix to this report and in the hearing record contain a more detailed treatment of these issues. These principles have been developed over a decade or more, and because they have been the product of extensive scientific and public review, they enjoy wide acceptance in the scientific community. The principles are not immutable, and they will no doubt change in time as scientific understanding of cancer causation increases. What they represent is the best scientific consensus of our time.

There are approximately 800,000 new cases of cancer each year. Cancer is now only second to heart disease as a cause of death in the United States, totaling some 400,000 deaths each year. Because the effects of cancer exact a high emotional and economic toll on society, and because cancer is often irreversible, prevention of cancer has become a major public policy goal.

The exact cause of most cancer is unknown and in fact most scientists now believe that cancer is multi-factorial; that is, it is probably caused by many factors. Analysis of world cancer mortality rates has led generally to the recognition that the total environment -- including life-style, personal habits, hormonal factors, and work and environmental factors -- plays a significant role in causing the majority of cancers and that cancer is not principally

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the legacy of genetic heritage.

Because some cancer is believed to be preventable, efforts to identify and control factors contributing to cancer have taken a high priority in government, and in the medical, public interest, labor and business communities as well.

The are four generally recognized acceptable methods for detecting and identifying potential carcinogens:

1. molecular structure analysis
2. short-term tests
3. long-term chronic bioassays in laboratory animals
4. epidemiology

Test results from such methods are not of equal weight in determining a substances carcinogenic potential. Table 1 sets out by type of test the scientific basis for each test, the time to undertake each test, and the results and conclusions drawn from each test.

Table 1—General Classification of Tests Available To Determine Properties Related to Carcinogenicity

Method	System	Time required	Basis for test	Result	Conclusion, if result is positive
Molecular structure analysis	"Paper chemistry"	Days	Chemicals with like structures interact similarly with DNA	Structure resembles (positive) or does not resemble (negative) structure of known carcinogen	Chemical may be hazardous. That determination requires further testing.
	Basic laboratory tests	Weeks			
Short-term tests	Bacteria, yeast, cultured cells, intact animals	Generally few weeks (range 1 day to 8 months)	Chemical interaction with DNA can be measured in biological systems	Chemical causes (positive) or does not cause (negative) a response known to be caused by carcinogens	Chemical is a potential carcinogen.
Bioassay	Intact animals (rats, mice)	2 to 5 years	Chemicals that cause tumors in animals may cause tumors in humans	Chemical causes (positive) or does not cause (negative) increased incidence of tumors	Chemical is recognized as a carcinogen in that species and as a potential human carcinogen.
Epidemiology	Humans	Months to lifetimes	Chemicals that cause cancer can be detected in studies of human populations	Chemical is associated (positive) or is not associated (negative) with an increased incidence of cancer	Chemical is recognized as a human carcinogen.

Interpretation and description of test results is of crucial importance in assessing whether a chemical is a potential carcinogen. Assuming well conducted tests, analysis of test results are conveniently discussed as being "positive", "negative", or "inconclusive". According to the Congressional Office of Technology Assessment (OTA), a "positive" test is sufficient to convince all (or most) experts that the tested substance causes the measured effect -- e.g., cancer in a bioassay -- and a "negative" result is

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5 Source: U.S. Congress, Office of Technology Assessment, Assessment of Technologies for Determining Cancer Risks from the Environment (June 1981) (hereinafter "OTA Report"). Table 23, p.114. While OTA acknowledges that no statement in the table is "free from dispute" it notes the general scientific acceptance of these statements. See Appendix E.

one that convinces all (or most) experts that the tested substance does not exert the effect measured in the test. "Inconclusive" means that no conclusion can be drawn from the test.[6]

While short term tests and bioassays are used to evaluate a chemical's carcinogenic potential in the laboratory, as can be seen from the above table, only epidemiology can directly assess the effect of a chemical exposure on humans. Well-conducted and properly evaluated epidemiology studies which show a positive association are accepted as the most convincing evidence about human risks. On the other hand, the value of a negative result is directly related to the "statistical power of the study", that is, the statistical ability of the study to measure the result looked for. For example, negative epidemiologic results may show that exposure of a certain number of people to a particular substance at a specified level does not result in an increased number of cancer cases. From such results it is possible to calculate that the human risk is not higher than what the study could have detected. For instance, a study of 1,000 people which showed no excess cancer would be "more negative" than one of 100 people exposed at the same level. Neither study would show that no risk exists, but the larger study would indicate a lower probability of risk.[7]

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6 OTA Report at 11.
7 OTA Report at 139.

How epidemiologic studies are interpreted is of major relevance to the Subcommittee's investigation since one of the issues the Subcommittee considered was the EPA characterization of the results of the epidemiologic studies on formaldehyde. While the Todhunter memorandum called or inferred that the studies were "negative", hearing witnesses and others concluded the studies were merely inconclusive. See discussions at pp. 41-44.

How animal studies are interpreted is also of major relevance to the Subcommittee's investigation since the Subcommittee also considered questions about EPA's objectivity in characterizing animal studies. There was disagreement between hearing witnesses and Dr. Todhunter on the interpretation of the results of animal studies. See discussion at pp. 50-52.

While the value of a positive epidemiologic test in evaluating the carcinogenic potential of chemicals is well recognized, the value of negative or inconclusive studies is subject to some, though not widespread, disagreement. Generally, epidemiology is a crude investigational tool and, at least in the past, federal agencies have tended, because of the inherent problems in epidemiological studies, to place little weight on an inclusive study and to consider a negative study of less importance than positive results in an

animal bioassay that is well-designed and well-conducted.[8]

The value of epidemiology in assessing carcinogenic potential was also of major relevance to the Subcommittee's investigation since the Subcommittee also considered the allegation that EPA, contrary to established policy and without peer or public review, placed great weight in its decision on the absence of positive epidemiological data, even in the presence of excellent animal data which very strongly demonstrated the carcinogencity of formaldehyde in animals.

As can be seen from table 1, a positive result in a well-conducted animal bioassay is generally interpreted to mean that the "chemical is recognized as a carcinogen in that species and as a potential human carcinogen." There is no doubt that this conclusion enjoys wide acceptance in the scientific community. For example, the International Agency for Research on Cancer (IARC), an agency of the World Health Organization, has concluded:"... it is reasonable, for practicable purposes, to regard chemicals for which there is sufficient evidence of carcinogenicity... in animals as if they presented a carcinogenic risk for humans." (emphasis in

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8 For example, "The OSHA position, and that of Federal Government regulatory agencies in general, is to use epidemiology to estimate limits of risk, but not to weigh negative human evidence against other positive evidence in deciding whether or not a substance is carcinogenic." OTA Report at 139 (footnote omitted).

original)[9]

Similarly the OTA Report concludes: "The last decade saw government organizations, Congress, executive agencies, and the courts, as well as private sector organizations endorse bioassays and agree that they can be used to identify potential human carcinogens."[10]

The presumption that an animal carcinogen should be treated as a potential human carcinogen is also of relevance to the Subcommittee inquiry since the Subcommittee reviewed the allegation that the EPA decision rejected the longstanding federal policy that agencies regard chemicals for which there is sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk to humans." (See discussion at pp. 30-34).

Table 2 contains a list of some of the organizations which have endorsed those principles.

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9 OTA Report at 128.

10 OTA Report at p. 11. See also, Perera, F. and Petito, C. "Formaldehyde: A Question of Cancer Policy?" Science, v. 216, p. 1285 (June 18, 1982) (hereinafter "Science") and the other reference contained in Appendices E and F.

Table 2 -Some Organizations That Have Considered and Endorsed Animal Tests as Predictors of Human Risk From Chemical Carcinogens

Organization	Publication
The Secretary's (HEW) Committee on Pesticides and their Relationship to Environmental Health	Report (325)
National Research Council	— Evaluating the Safety of Food Chemicals (259) — Safety of Saccharin and Sodium Saccharin in the Human Diet (261) — Pest Control: An Assessment of Present and Alternative Technologies (262) — Principles for Evaluating Chemicals in the Environment (263) — Food Safety Policy (269)
Office of Technology Assessment	— Cancer Testing Technology and Saccharin (282) — Environmental Contaminants in Food (284)
National Cancer Advisory Board, Subcommittee on Environmental Carcinogenesis	— General Criteria for Assessing the Evidence for Carcinogenicity of Chemical Substances (245) — The Relation of Bioassay Data on Chemicals to the Assessment of the Risk of Carcinogens for Humans Under Conditions of Low Exposure (246)
American Industrial Health Council	— AIHC Recommended Alternative to OSHA's Generic Carcinogen Proposal (8)
Food Safety Council	— Proposed System for Food Safety Assessment (125)
Occupational Safety and Health Administration	— Identification, Classification and Regulation of Potential Occupational Carcinogens (279)
Interagency Regulatory Liaison Group	— Scientific Bases for Identification of Potential Carcinogens and Estimates of Risks (180)
Office of Science and Technology Policy	— Identification, Characterization and Control of Potential Human Carcinogens: A Framework for Federal Decision-making (281)
American Federation of Labor, Congress of Industrial Organizations, and United Steelworkers of America	— Post-Hearing Brief on OSHA's Proposed Standard on the Identification, Classification and Regulation of Toxic Substances Posing a Potential Occupational Carcinogenic Risk (7)

Source: OTA Report at 129 (Table 28)

Chronology of EPA Decision

The single most significant study on the carcinogenicity of formaldehyde was undertaken by the Chemical Industry Institute on Toxicology (CIIT), a testing institute funded by the chemical industry. The bioassay, begun in June 1978 involved 1,920 animals. The preliminary results of the study, which generally demonstrated the carcinogenic properties of formaldehyde at certain dose levels and in

certain species, were reported by CIIT to EPA in October, 1979 because CIIT believed the results were so significant that section 8(e) of the Toxic Substances Control Act may have required that it be expeditiously reported to EPA. The results were widely reported in the press shortly thereafter and major public and regulatory concern about the carcinogenic risks of formaldehyde dates from this time period. Since the chronology of events leading to EPA's decision is important to the understanding of the allegations of bias made against EPA, a brief chronology of relevant events follows:

Chronology

Fall 1979	CIIT notification of preliminary data to EPA.
	At the request of CPSC the National Toxicology Program convened a panel of Federal scientists to review the data on formaldehyde.
November 1980	Federal panel concludes that "formaldehyde should be presumed to pose a carcinogenic risk to humans."
Nov. - May 1981	EPA staff reviews data and develops recommendation to consider formaldehyde for priority action under Section 4(f).
May 1981	EPA staff recommendation on applicability of action on formaldehyde under 4(f) reaches Administrator Gorsuch, approximately 180 days after notification to EPA of the Federal Panel's conclusions.[11]

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11 See footnote 1. Section 4(f) specifically requires the Administrator to initiate appropriate action under the Act (Footnote continued)

	Administrator Gorsuch asks Dr. John Hernandez, Deputy Adminstrator, to reevaluate the scientific data on formaldehyde.
June, July, & August 1981	Dr. Hernandez convenes three closed-door "science-courts" to consider data on formaldehyde. Attendance, by invitation only, includes lawyers and scientists representing primarily EPA and the Formaldehyde Institute and CIIT. Additional attendees at some meetings include representatives from the NAS and ORNL.
September 1981	Memorandum from Don Clay, Director of EPA's Office of Toxic Substances, to John Todhunter recommending against consideration of formaldehyde under section 4(f), accompanied by options paper based on PRL-1, science courts, and other staff analyses.
November 1981	Technical Document appears (based on PRL-1, revised under supervision and direction of Dr. Todhunter).
February 1982	Memorandum to Anne Gorsuch from John Todhunter through John Hernandez recommending against consideration of formaldehyde under section 4(f).

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11 (continued)
or to explain his decision not to act, within 180 days of receipt of specified test data, 15 U.S.C. § 2603(f).

WITNESS LIST

Thursday May 20, 1982 — 2318 Rayburn House Office Building

Panel 1
Scientific Review

Dr. Norton Nelson
Professor of Environmental Medicine
Institute of Environmental Medicine
New York University Medical Center

Dr. Roy Albert
Professor of Environmental Medicine
Deputy Director and Vice-Chairman of the Institute of Environmental Medicine
New York University Medical Center

Dr. Kenny Crump
President
Science Research System, Inc.

Dr. Richard Griesemer
Director, Biology Division
Oak Ridge National Laboratory

Panel 2
Consumer Product Safety Commission Perspective

Dr. Peter Preuss
Associate Executive Director, Health Sciences
U.S. Consumer Product Safety Commission

Dr. Andrew Ulsamer
U.S. Consumer Product Safety Commission

Dr. Murray Cohn
U.S. Consumer Product Safety Commission

Panel 3
U.S. Environmental Protection Agency Perspective

Dr. John Todhunter
Assistant Administrator for Pesticides and Toxic Substances
U.S. Environmental Protection Agency

Mr. William Petersen
Office of General Counsel
U.S. Environmental Protection Agency

Mr. Donald Clay
Director, Office of Toxic Substances
U.S. Environmental Protection Agency

Panel 4
Extra-governmental Viewpoints

Mr. Richard Dailey
Former employee, Environmental Protection Agency

Dr. Frederica Perera
Senior Staff Scientist
Natural Resources Defense Council

Ms. Jacqueline Warren
Senior Staff Attorney
Natural Resources Defense Council

Panel 5
Witnesses Requested by the Minority

Dr. James Gibson
Vice-President and Director of Research
Chemical Industry Institute of Toxicology

Dr. Robert Sielken, Jr.
Texas A and M University

Dr. Sorell Schwartz
Professor of Pharmacology
Georgetown University

SUMMARY OF CONCLUSIONS AND RECOMMENDATIONS

I. Issue: Did EPA depart from traditional and widely supported principles for carcinogenic risk assessment in its formaldehyde decision? If so, has EPA articulated valid scientific reasons for departing from well-established principles?

Findings:

1. EPA's decison (Todhunter memorandum) departed from traditional and widely supported principles for carcinogenic risk assessment in that:

(a) It concludes that a well conducted and properly designed animal bioassay that is positive in one (or two) species is not sufficient to regard a chemical substance as presenting a carcinogenic risk to humans.

(b) It concludes that positive human evidence (epidemiology) is necessary to regard an agent as a likely human carcinogen, and

(c) It concludes that there is a safe threshold for a carcinogen.

2. The scientific arguments articulated by Dr. Todhunter in support of the EPA decision generally raise issues that were considered and rejected in establishing the cancer principles. Dr. Todhunter's memorandum does not appear to rely on any new scientific data or raise any new or widely accepted interpretation of any theory that would justify departure from these principles.

II. Issue: Were the procedures used by EPA to obtain and interpret scientific data and to review the scientific basis of its decision undertaken in a manner so as to preserve the integrity of the scientific process at EPA and to enhance the credibility of its decision in the case of formaldehyde.

Findings:

(3) The absence of opportunity for peer review either within EPA or externally, or public review, raises serious questions about EPA procedures for obtaining and interpreting scientific data and about the validity of EPA's scientific reasoning and conclusions.

(4) EPA acted improperly or at a minimum created the appearance of impriority or bias by:

o Organizing closed-door "science courts" to which

only EPA staff, and lawyers and scientists primarily representing the affected industry were invited for the purpose of reviewing the data on formaldehyde.

o Changing or disregarding agency scientific staff interpretations of data without explanation or any apparent scientific justification.

o Incorporating opinions and non-peer reviewed data from the affected industry without appropiate review.

III. Issue: Does the EPA decision document present a balanced and scientifically defensible interpretation of the data on the potential carcinogenity of formaldehyde?

Findings:

(5) The February 10 memorandum does not present a balanced interpretation of the data on formaldehyde or discussion of the human carcinogenic potential of formaldehyde. The memorandum (1) characterizes the epidemiologic data as negative, when in fact the great weight of scientific opinion has concluded that the data is merely inconclusive; (2) characterizes certain animal studies as negative,

when in fact the studies have been found to be either methodologically flawed or designed for purposes other than detection of cancer; (3) appears to rely on theories for the carcinogenic mechanism for formaldehyde which are at variance with both the weight of scientific opinion generally and the data on formaldehyde; and (4) inaccurately characterizes federal regulatory policy on action levels for federal concern.

Based on these findings, the Subcommittee makes the following recommendations:

1. That the traditional principles for carcinogenic risk assessment be followed by EPA until such time as they are caused to be modified by new scientific findings, and then only after a reasonable opportunity for peer and public review.

2. That the scientific basis of EPA decisions not to regulate a substance, because such decisions can have as great an impact on the public health as decisions to regulate can have on the affected industry, be subject to adequate and impartial scientific review within, and where appropriate, outside the agency.

EXPLANATION OF FINDINGS AND RECOMMENDATIONS

1. ISSUE: Did EPA depart from the traditional and widely supported prinicples for carcinogenic risk assessment in its formaldehyde decision? If so, has EPA articulated valid scientific reasons for departing from well established principles?

Findings:

1. EPA's decision (Todhunter memorandum) departed from traditional and widely supported principles for carcinogenic risk assessment in that:

(1) It concludes that a well-conducted and properly designed animal bioassay that is positive in one (or two) species is not sufficient to regard a chemical substance as presenting a carcinogenic risk to humans.

(2) It concludes that positive human evidence (epidemiology) is necessary to regard an agent as a likely human carcinogen, and

(3) It concludes that there is a safe threshold for a carcinogen.

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2. The scientific arguments articulated by Dr. Todhunter in support of the EPA decision generally raise issues that were considered and rejected in establishing previous cancer principles. Dr. Todhunter's memorandum does not appear to rely on any new scientific data or raise any new or widely accepted interpretation of any theory that would justify departure from these principles.

As discussed in pages 9-18 of this report, near universal support for the principles of carcinogenic risk assessment exist in the scientific and regulatory community. The principles include the following general assumptions:

- Properly designed and conducted tests using appropriate animal species are accepted as a valid way to identify chemical substances that may cause cancer in humans.

- Positive human data are not necessary to regard an agent as a potential human carcinogen.

- It is not now possible to extrapolate from animal data to a "safe" population threshold for any carcinogen regardless of the mechanism of action.

The principles have gained wide credibility over time and have been supported by public and peer review. Drs. Nelson, [12] Albert,[13] Crump,[14] Griesemer,[15] Perera,[16] Upton,[17] Weinhouse,[18] and others uniformally supported the general notion as well as the conclusion that on the available data formaldehyde should be treated as a potential human carcinogen. For example Dr. Upton, former director of the National Cancer Institute stated:

> To compare our views on this subject with those of our colleagues, we have consulted several of the world's leading authorities on chemical carcinogenesis for their opinions. The replies we have received from them thus far are unanimous in supporting the principle that definitive demonstration of carcinogenicity in well-conducted animal bioassays suffices to provide evidence of presumptive carcinogenicity for the human population.[19]

And Dr. Schwartz, who testified at the specific request of the minority, concurs in large measure:

> [Formaldehyde] is in fact demonstrated to be an animal carcinogen, and my own personal philosophy is that if

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[12] Hearing Record at 20-23.

[13] Ibid, at 73, 80-81.

[14] Ibid, at 37.

[15] Ibid, at 64.

[16] Ibid, at 172.

[17] Ibid, at Appendix 7.

[18] Ibid, at 11-19.

[19] Ibid, at Appendix 7.

> something is demonstrated to be an animal carcinogen, irrespective of all theoretical considerations, it must be, at this particular time, for reasons of prudence, to be considered as a human carcinogen.[20]

Dr. Todhunter's reply to questions asked by the Members of the Subcommittee at the hearing appears to contradict the position taken in his memorandum, on at least the first two points. Dr. Todhunter stated:

> The second misconception is that EPA has somehow departed from longstanding principles of risk assessment in developing its position on formaldehyde. The fact is, EPA considers formaldehyde to be a carcinogen in the rat by the inhalation route, possibly also in the mouse by the same route, and EPA presumes that formaldehyde may, in theory, pose a risk of cancer to humans. EPA also holds that animal testing, carefully analyzed, is an appropriate indicator of potential human risk.[21]

* * * * * * *

> MR. GORE: Well, you referred to the IARC group a moment ago. Let me just read you their statement: "In summary, then, the IARC working group has declared that formaldehyde must be regarded as if it were carcinogenic to man on the basis of toxicological studies in animals."
>
> DR. TODHUNTER: We would agree with that. We certainly would, and that is why we went out and did all the way along, we have done risk analysis on it. If we did not think it was carcinogenic to man, if we did not think it had the potential, let us say, we would not bother to spend staff time to work these models over.[22]

These statements should be compared with the statements

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[20] Ibid, at 236.
[21] Ibid, at 110.
[22] Ibid, at 148.

and tone throughout the memorandum which tend to underemphasize the importance of the positive animal data on formaldehyde, and overemphasize the absence of positive epidemiological data in reaching its conclusion. [23]

Dr. Todhunter's memorandum also appears to accept the argument that there is an exposure threshold or safe dose for formaldehyde.[24]

Dr. Todhunter postulates a mechanism of carcinogenicity for formaldehyde that depends upon irritation as a prerequisite to tumors. Hence, he concludes that a low dose that does not produce irritation is a safe dose. Dr. Todhunter acknowledges in his testimony that the source of the data he used to draw his conclusions came in part from conversations with CIIT (Dr. Swenburg) and that he did not look at the data himself.[25]

Dr. Todhunter's conclusion is based on a theoretical assumption that a threshold can be defined for carcinogens, a position that has been widely, though not totally rejected in the scientific community. His conclusion also stems from his view of the CIIT data on formaldehyde that is not shared by most of the witnesses on the record. For example, Dr. Griesemer stated:

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23 Appendix B. Cf. See testimony of Drs. Griesemer and Perera generally.
24 Appendix B.
25 Hearing Record, at 147-148.

> The only evidence that there may be a threshold for carcinogenicity is that small amounts of formaldehyde are found normally in the body. The practical threshold therefore is the endogenous level of formaldehyde and any additional exposure from exogenous sources can be considered to increase the risk of cancer. [26]

Dr. Perera stated:

> ...the observation by Dr. Todhunter that tumors appear to be secondary to cell injury triggered only at high levels of exposure ("simply put, the animals developed open sores in their nasal tissues after which tumors appeared") is contrary to these expert reviews.[27]

Similarly Dr. Nelson stated:

> In the discussion of the carcinogenicity of formaldehyde, much has been made of the irritant properties of formaldehyde. This is a red herring in which the implication is that irritancy was crucial to the development of carcinogenicity. In our studies at NYU in rats exposed both to formaldehyde and hydrochloric acid (HCl), a known very potent irritant, no greater increase in cancer was observed than in rats exposed to formaldehyde alone, nor was cancer found in any of the animals exposed to HCl alone.[28]

And Dr. Nelson further stated:

> Let me say a few words about thresholds which also receive extensive discussion in Dr. Todhunter's memorandum. In his memorandum there is the implication that there may be, and perhaps are, thresholds for formaldehyde which would make human exposures to lower levels negative and inconsequential. This cannot be accepted without comment. In the first place, the usual studies using laboratory animals with groups of manageable size are relatively insensitive for measuring dose response relationships, and are normally quite incapable of detecting thresholds. It is very chancy to attempt to depend exclusively on such data for estimating the risk to humans. I am in

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26 Ibid, at 63.
27 Ibid, at 178.
28 Ibid, at 31.

> favor of using quantitative risk assessments, but such use must be done judiciously and with a clear recognition of quantitative limitations; our science is simply not skilled enough to permit precise estimates of risk in these instances. In addition, the assumption of the threshold is widely regarded in the scientific community as being an imprudent assumption for public health protection. The basic issues are rather simple. The demonstration of a threshold in animal studies would be a feat of major proportions, extraordinarily difficult, expensive, and of uncertain outcome.
>
> * * * * * *
>
> We must accept the fact that a demonstration of a practical threshold in humans or in animals is likely to be difficult and elusive and, at the present time, probably not attainable.
>
> Any biologist working in these fields can dream of several scenarios describing biological action of carcinogens which would postulate the presence of a threshold. And there may well be practical thresholds for some chemicals. On the other hand, there are even more persuasive biological grounds for thinking that in many cases, perhaps the great majority, there will be no threshold. Since the practical demonstration of a threshold is difficult, often impossibile, a prudent course for purposes of public health control is to assume that there is no threshold.[29]

The testimony of Dr. Gibson of CIIT, who was specifically requested to testify by the minority, does not support Dr. Todhunter's interpretation either. The following exchange between Chairman Gore and Dr. Gibson is illustrative:

> MR. GORE: Dr. Todhunter appears to believe that. Now maybe I am misrepresenting his view but the memo appears to indicate a view that the irritation necessarily preceded the cancer in the rat study,

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29 Ibid, at 33-34.

and that the inference he drew was that it was a causal factor.

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MR. GORE: However, you are just saying that there is a correlation. You are not saying that without irritation leading to cell injury and proliferation, cancer cannot develop.

DR. GIBSON: No, I am not saying that.[30]

II. ISSUE: Were the procedures used by EPA to obtain and interpret scientific data and to review the scientific basis of its decision undertaken in a manner so as to perserve the integrity of the scientific process at EPA and to enhance the credibility of its decision.

Findings:

(1) The absence of any opportunity for peer review either within EPA or externally, or public review, raises serious questions about EPA procedures and about the validity of EPA's scientific reasoning and conclusions.

(2) EPA acted improperly or at a minimum created the appearance of impriority or basis by:

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30 Ibid, at 241. The testimony of Dr. Albert further supports this position at p.70.

- o Organizing closed-door "science courts" to which only EPA staff, and lawyers and scientists primarily representing the affected industry were invited for the purpose of reviewing the data on formaldehyde.

- o Changing or disregarding agency scientific staff interpretations of data without explanation or any apparent scientific justification.

- o Incorporating opinions and non-peer reviewed data from the affected industry without appropriate review.

A major issue throughout the hearing was a question about the source of the data and advice Dr. Todhunter depended on in writing his memorandum. Allegations were made about secret EPA-industry meetings and about rejection of staff analysis in favor of non-peer reviewed data submitted by CIIT or the Formaldehyde Institute. While it is clear that the Todhunter memorandum contains both interpretations of data, and opinons, including those on the carcinogenic mechanism for formaldehyde, not found in the PRL-1 or staff technical documents, the exact source of many of the

inconsistencies in data and opinion is not clear. There is some support in the record for the proposition that they come from either the Formaldehyde Institute or CIIT.[31]

While Dr. Todhunter generally denied that his interpretation of the science differed from that of his staff or that he insisted upon unsupported changes in interpretation of data, [32] he did acknowledge that he did not accept all of the reasoning of his staff,[33] and he further acknowledged that some of the data, at least, came from the Henandez science courts and from personal conversations with "Dr. Heck and Dr. Swenburg at CIIT."[34]

Perhaps the reason for the apparent inconsistencies is, as Dr. Todhunter explained in reply to Chairman Gore, that his document was not the agency decision document and also not the careful scientific explanation it had been treated as, but was intended as an explanation to the lay person of the science and rational for EPA's decision. There is substantial evidence that indicates that whatever may in fact have been Dr. Todhunter's intention, EPA's Deputy Administrator, Dr. Hernendez, and EPA generally seem to have

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[31] Ibid, at 130, 134-135. See also Appendix 12.

[32] Ibid, at 129-130.

[33] Ibid, at 135-136.

[34] Ibid, p. 130, 134-135.

regarded the document as a scientifically justifiable document articulating the agency's position on formaldehyde.[35] The other implication to be drawn from Dr. Todhunter's statement to the Subcommittee -- that a public health official could expect to circulate widely an explanation of a major controversial regulatory decision and not anticipate careful scrutiny -- is equally troubling.

External and Peer Review

Dr. Todhunter acknowledges that his document was not reviewed by his science advisor nor by anyone else on his staff before it was sent to the administrator.[36] While Dr. Todhunter denies discussing his memorandum with anyone outside EPA prior to its transmission to the Adminstrator, he acknowledges discussing significant conclusions with the CIIT prior to writing the memorandum. [37]There is no evidence in the record that the Todhunter memorandum received any scientific review prior to being publicly released by EPA.

Hernandez Science Courts

At the request of the EPA Administrator, Dr. John

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[35] See Appendix C.

[36] Hearing Record, at 132-133.

[37] Ibid, at 130,134.

Hernandez, Deputy Administrator at EPA reviewed the data on formaldehyde. During June, July, and August 1981, Dr. Hernandez convened a total of three so-called science courts to review the data on formaldehyde. Specific EPA staff were invited to attend the meeting as were lawyers and scientists representing the formaldehyde industry and CIIT. Additionally Dr. Griesemer attended two meetings and representatives from the National Academy of Sciences attended one or two meetings.[38] According to the unrebutted and unchallanged testimony of one witness, a request that scientists from the Occupational Safety and Health Administration (OSHA) and CPSC be included was rejected by EPA.[39] There was no public announcement of the meeting, no published agenda or generally publicly available record of the proceedings. While Dr. Hernandez and others may have considered the "courts" to be a useful forum to obtain data, the lack of balance in the perspectives held by those invited, the absence of public input, and the secrecy surrounding the meetings at a minimum create the impression that the meetings were biased and could have improperly influenced the final EPA decision.

Rejection of EPA Staff Analysis and Use of Non-Peer Review Data

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[38] Hearing Record, Appendix 8.

[39] Ibid, at 168, 206-207.

Perhaps one of the most serious allegations raised at the hearing was that Dr. Todhunter unjustifiably rejected staff analysis of data and substituted in place thereof non-reviewed scientific data and opinion supported by the industry and not generally supported by the scientific community, and that Dr. Todhunter sought to force employees improperly to change scientific conclusions. There is some testimony and documentary evidence to support these allegations.

The dispute over the use and interpretations of the CIIT data on free formaldehyde in the human body is an illustration of the concerns expressed above. The question of free formaldehyde is of major significance in Dr. Todhunter's conclusion that there is a high human threshold for formaldehyde's carcinogenic effect.

The Todhunter memorandum concludes (p.8) that normal tissue contains significant levels of free formaldehyde. This data does not appear in either the PRL-1 or Technical Document. It is in distinct contrast to the Federal Panel Report on Formaldehyde which concluded that "free formaldehyde is not usually found in plasma or other body tissues in measurable quantities" and is also in contrast with the testimony of Drs. Todhunter,[40] Preuss,[41] and Griesemer.[42]

Support for this position in the record can be found only in positions advocated by the Formaldehyde Institute and by CIIT.[43]

Mr. Dailey provided the Subcommittee with the following explanation of the origin of the data in the Todhunter memorandum:

> In October of 1981, I was given a copy of the PRL-1 with changes to be made that had been penciled in by Dr. Todhunter. I questioned some of the changes that were to be made but was ordered to incorporate Dr. Todhunter's comments verbatim. One particular example stands out as illustrative of my reluctance to make the requested revisions.
>
> During the course of the Hernandez meetings, Drs. Hernandez and Todhunter emphatically stated that for the Agency to maintain scientific credibility, staff scientists, in preparing technical documents should adhere to the traditional demands of scientific rigor. They implied that only under special circumstances should data that has not received traditional peer review be used. However, at one of the Hernandez meetings, Dr. Heck, a researcher from CIIT, indicated that preliminary results from his work indicated that 3ppm formaldehyde could be found in the nasal mucosa of unexposed rats. Dr. Heck implied that this was free formaldehyde. During a break in the meeting, I asked Dr. Heck if it was not, in fact, more likely that formaldehyde was found as an adduct to tetrahydrofolate or glutathione, and therefore unavailable for interaction with a cellular constituent. He stated that this was probably true and we apprised Dr. Hernandez of that fact.

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[40] Ibid, at 143-144.

[41] Ibid, at 83.

[42] Ibid, at 56, 71.

[43] Ibid, at 143-144.

One of Dr. Todhunter's revisions, however, stated that up to 3ppm endogenous formaldehyde had been found in the nasal mucosa of rats not exposed to formaldehyde, citing Dr. Heck in 1981. He stated that one could conjecture that 3ppm would be a threshold below which one would not expect cancer induction.

I then called Dr. Heck at CIIT and asked if, since Dr. Todhunter's reference was of the type typically used for published literature, his paper on endogenous formaldehyde had been published. He replied no, and that it was not even in proper form to be sent to a journal for consideration. I then asked if anybody at the Agency was in receipt of any personal communication from him stating the results of his findings. He answered that negatively also. I then asked him, in his best estimate, how much of the endogenous formaldehyde (3ppm) that he had mentioned to Dr. Hernandez would actually be free formaldehyde. He replied that at least 90% would be found as adducts.[44]

Dr. Todhunter acknowledges that he participated in the changes in substance on certain "biological molecular aspects" and that the source of the information he provided to EPA staff was a variety of references and personal communication with Dr. Heck and Dr. Swenburg at CIIT.[45]

However, Dr. Todhunter generally denied that he forced EPA employees to incorporate his changes in the technical document.[46]

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44 Hearing Record at 168-169. The PRL-1 referenced in Mr. Dailey's testimony is the "Priority Review Level-1: Formaldehyde" of February 19, 1981. The PRL-1 was developed by EPA's Office of Toxic Substances to provide supporting documentation for its recommendation to the EPA Administrator that formaldehyde be considered for priority action under Section 4(f). Subsequent revisions to the PRL-1 were called "The Technical Document on Formaldehyde" (TD). The first TD appeared on November 16, 1981. A subsequent revision appeared in March 1982, after Dr. Todhunter's decision. At the time of the Subcommittee's hearing, the TD was still under review.

45 Ibid, at 129-130, 134-145.

46 Ibid, at 130.

The PRL-1 does contain Dr. Todhunter's pencilled-in revisions suggesting that free formaldehyde exists,[47] and the November 16, 1981 revision of the technical document does include such changes.[48]

Further support for the general allegations are provided in the discussions pertaining to the evaluation of the epidemiological data on formaldehyde.

Dr. Todhunter concluded that "there is a limited but suggestive epidemiological data base which supports the notion that any human problems with formaldehyde carcinogenicity may be of low incidence or undetectable. It would not appear reasonable to say that a significant risk situation exists from the data."[49]

Assuming the epidemiological data base is built on well-conducted studies, a negative epidemiological study can only establish a negative inference within the statistical power of the study. Not only does Dr. Todhunter imply that the epidemiologic data base is negative (rather than inconclusive) but he seems to have also concluded -- overbroadly -- from the epidemiology that the carcinogenic risk to humans from formaldehyde is not significant.[50]

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47 Hearing Record, Appendix 3.
48 Ibid.
49 Appendix B.
50 Dr. Todhunter's position can be compared with that of
(Footnote continued)

In contrast to the conclusions to be drawn from Dr. Todhunter's statements on the epidemiology, the EPA staff characterized the epidemiology in the following manner:

> "This lack of a pattern, the lack of precise information concerning the number of persons exposed to formaldehyde and the level of exposure, and problems of confounding exposures, make it difficult to interpret these reports. Findings of excess cancers among workers in occupations and industries associated with formaldehyde and other chemicals raises concern that formaldehyde may be a carcinogen."[51]

The OTS Options memorandum, and the November 16th revision to the technical document provided additional support for the proposition that Dr. Todhunter changed or did not rely on the staff interpretation of the epidmiologic data.[52]

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[50] (continued)
the Formaldehyde Institute. "Three epidemiology studies presented at CIIT are in agreement that there is no excess in nasal or respiratory cancer or even a significant increase in any form of cancer which would be attributed to formaldehyde. Although the individual studies may be limited in scope, when combined they clearly indicate no increased cancer in the exposed population. Additional informal reviews of large numbers of workers exposed to formaldehyde have not shown an increase of nasal or paranasal cancers, and no other cancers have been attributable to formaldehyde exposure. (letter from Joel Bender, Chairman, Medical Committee, Formaldehyde Institute, to Thorne Auchter, Assistant Secretary, OSHA, August 28, 1981, with carbon copies noted to Mrs. Gorsuch and Dr. Hernandez. A further discussion of this issues appears on pp. 49-50.

[51] Hearing Record, at 136.

[52] Ibid, Appendix 12. The OTS Options memorandum, September 9, 1981, was prepared by EPA's Office of Toxic Substances at the request of Don Clay, Director of EPA's
(Footnote continued)

Dr. Todhunter acknowledges his disagreement with his staff but offers no explanation as to why he failed to follow the staff's characterization or why his alternative is more supportable.[53]

In the November 16 draft of the Technical Document, the staff commented on the epidemiological data as they had in the earlier PRL-1 document: "the lack of a pattern and precise data in the epidemiological data, make it difficult to interpret these reports." Dr. Todhunter then added these comments: "It is safest to say that the available human evidence does not indicate that formaldehyde poses a significant hazard, but it does not rule out any or all hazards."[54]

Apparently the staff did not agree with Dr. Todhunter's comments, since they were scratched out.

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[52](continued)
Office of Toxic Substances, following "The series of meetings between EPA and the Formaldehyde Institute that Dr. Hernandez conducted." The memorandum summarized the data on formaldehyde and EPA's options for action. The memorandum was transmitted to Dr. Todhunter together with Mr. Clay's recommendation on September 11, 1981. The options memorandum rejected the Formaldehyde Institute's argument that, based on the epidemiology data, "formaldehyde did not present a risk of cancer to humans" and concluded that the data are "inconclusive". Options memoranda, pp. 16-17. Similarly, the November 16, 1981 Technical Document stated, "... the lack of a patern and precise data on the epidemiological data make it difficult to interpret these reports." Hearing Record, Appendix 3.

[53] Ibid, at 135-137.

[54] Ibid, at Appendix 3.

There are additional examples of the rejection of staff opinion without apparent scientific support or explanation. For example, Ms. Warren addressed the revisions in the Technical Document containing discussions on the interpretation of the CIIT results (p. 86-90) which strongly suggest a threshold exists for carcinogenicity of formaldehyde. Dr. Todhunter's insertions in the PRL-1 discussion of previous ("negative") bioassays of formaldehyde tend to lend them greater importance than in the PRL-1 and tend to qualify the relevence of the CIIT study to humans.[55]

III. ISSUE: Does the EPA decision document (Todhunter memorandum) present a balanced and scientifically defensible interpretation of the data on the carcinogenic potential of formaldehyde?

Finding: The EPA decision document is not a reasoned scientific interpretation of the data on formaldehyde. Among other things it consistently interprets data in a manner so as to underestimate the carcinogenic potential of formaldehyde. For example, (1) it characterizes the epidemiologic data as negative, when in fact the great weight of scientific opinion has concluded that the data is merely inconclusive; (2) it characterizes certain animal studies as negative, when in fact the studies have been found to be

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[55] Ibid, at 196-197.

either methodologically flawed or designed for purposes other than detection of cancer; (3) it appears to rely on theories for the carcinogenic mechanism of formaldehyde which are at variance with both the weight of scientific opinion generally and the data on formaldehyde; (4) it inaccurately characterizes federal regulatory policy on action levels for federal concern.

The witnesses at the hearing were in near unanimity in questioning the objectivity of the presentation of the science in the Todhunter memorandum. For example, Dr. Roy Albert, Deputy Director of the Institute of Environmental Medicine at New York University and head of EPA's Scientific Advisory Board's Committee on Carcinogenic Risk Assessment, stated:

> I am reasonably sure that the February 10, 1982 Todhunter formaldehyde document was not reviewed by scientists within the EPA or the Science Advisory Board. All of the faults of this document, I believe, can be ascribed to the short circuiting of the scientific review process.
>
> The Todhunter formaldehyde document was written in support of a regulatory decision. The exposition of the science was clearly tailored to fit the decision. The document is far too one-sided to be regarded as a balanced assessment of the cancer risks from formaldehyde.[56]

And Dr. Norton Nelson, a preeminent authority on carcinogenic risk assessment, stated:

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56 Ibid, at 36.

> I might parenthetically add that the Todhunter memorandum is in some ways a remarkable document which goes through a series of biological issues, point by point, some highly relevant, some less relevant, and in each case concludes that in the judgment of the writer of that memorandum, the evidence does not merit the regulation of formaldehyde under EPA legislation. I say the document is remarkable in the sense that in each issue examined, an extreme position is taken relating to the probable non-significance of the data on formaldehyde. It would perhaps be understandable for such an analysis to be prepared by industry or a manufacturing firm using formaldehyde. To be put forward as a dispassionate examination of evidence by a public agency responsible in this country for protecting the health of the public from such agents must be viewed as irresponsible. Obviously, such an evaluation clearly violates the principles which have been promulgated and widely accepted as based on a prudent concern for protecting the health of the public.[57]

Dr. Schwartz, noted under questioning from Chairman Gore that, "...I do not agree with all of his [Dr. Todhunter's] science..."[58]

The data on formaldehyde's carcingenicity has been vigorously peer reviewed by numerous groups and individuals. The uniform conclusion is that formaldehyde is carcinogenic in rats (probably in mice) and should be treated as though it were a potential human carcinogen. Past analysis of the formaldehyde test data stand in stark contrast to the discussion of the data contained in Dr. Todhunter's memorandum.

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57 Ibid, at 29.
58 Ibid, at 239.

The following points are illustrative of the lack of balance in the Todhunter document and of the divergence between the majority viewpoints and those expressed in the Todhunter document.

o Characterization of Epidemiological Data

Dr. Todhunter's memorandum has been widely interpreted to suggest that the epidemiological data are negative when witnesses and other scientific experts consider it merely inconclusive.

For example, Dr. Preuss testified:

> Finally, it should be noted that a working group appointed by the International Agency for Research on Cancer, a part of the World Health Organization, concluded that:
>
> > 'The epidemiological studies provide inadequate evidence to assess the carcinogenicity of formaldehyde to man. In the absence of adequate epidemiological data, formaldehyde gas should be considered, for practical purposes, as if it represented a carcinogenic risk to man (IARC, 1981).[59]

Dr. Preuss was far more detailed in his own assessment of the data:

> At the present time, the available epidemiological studies of humans exposed to formaldehyde vapor are inadequate to assess its carcinogenic potential.

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59 Ibid, at 95-96.

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These studies, however, all suffer from problems which prevent them from coming to any definitive conclusions regarding the carcinogenic potential of formaldehyde in humans. These include:

(1) The studies were not large enough, and therefore statistically powerful enough, to be sure of the ability to detect a significant carcinogenic response;

(2) The duration and amount of (concentration in air of) exposure is not known;

(3) Cohorts were not always followed long enough to allow cancer to develop;

(4) It is not clear if all workers of these cohorts were known to actually have been exposed to formaldehyde.[50]

Similar statements were made by Drs. Weinhouse,[61] Perera, [62] Nelson,[63] and Griesemer.[64] In fact EPA's staff epidemiologist voiced the same criticism and reached the identical conclusions as to the value of the epidemiological study.[65] The Subcommittee could on the other hand find no support in the transcript for Dr. Todhunter's interpretation.

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60 Ibid, at 93-94.

[61] Ibid, at 11.

[62] Ibid, at 178.

[63] Ibid, at 31-32.

[64] Ibid, at 64.

[65] Ibid, at 137. See also discussion on pp. 34-45, infra.

o Characterization of Animal Bioassays

On Pages 6 and 7 of his memorandum, Dr. Todhunter characterizes the animal test data on formaldehyde, other than the CIIT study, as generally negative, and draws the conclusion that "there appears to be a high degree of species specificity and a strong dependence on the route of exposure."

According to the witnesses at the hearing, and others, such an interpretation is not accurate and tends to mischaracterize the animal studies, understate the relevance of the positive animal studies, and, hence, the conclusion that formaldehyde is a potential human carcinogen. For example, Dr. Griesemer stated:

> Dr. Todhunter implies further that the significance of the production of nasal tumors in rats is weakened by the results of other animal studies. On pages 6 and 7 of his memorandum he refers to other formaldehyde bioassays in such a way as to state that there appears to be a high degree of species specificity and a strong dependence on the route of exposure. Neither conclusion is supported by the facts. Mice have not been tested adequately for carcinogenicity. In the only study in mice by the Chemical Industry Institute of Toxicology (5), early mortality from fighting and other competing causes of death reduced the numbers of male mice that were at risk to developing cancers late in life. Even so, the statistical analysis of nasal carcinomas in male mice in the high dose group, when adjusted for early deaths, revealed a P-value of .0574, essentially the same as the level of significance of .050. Studies in hamsters thus far have not been designed to detect the carcinogenicity of formaldehyde but rather to fulfill other research objectives. Accordingly,

> the noses of experimental hamsters have not been systematically and thoroughly examined and the animals have not survived long enough and in large enough numbers for definitive conclusions to be reached. It should be mentioned that acetaldehyde, a substance with a chemical structure similar to formaldehyde, produces cancers of the nose and larynx in hamsters. The statement in the memorandum that the rat is unusually sensitive to the carcinogenic effects of formaldehyde is not supported by the data. Regarding routes of exposure, formaldehyde itself has only been tested adequately by the inhalation and subcutaneous routes and both are positive. From the available data, it is likely that no matter what the route of exposure formaldehyde would exert its greatest carcinogenic effect at the portal of entry where the dose delivered to the tissues would be the highest.[66]

In a review of the EPA's decision published in Science, the well respected peer review journal of the American Association for the Advancement of Science, Dr. Perera stated:

> "The prior reports of negative results in three long-term inhalation studies of formaldehyde do not detract from the significance of the CIIT and NYU studies. According to the NTP report (14), all three had shortcomings in experimental protocols and execution (for example, high mortality, inadequate exposure, or deficient histopathology). Bioassays in which other routes of exposure were used have been similarly limited; however, some give definite clues that formaldehyde may be carcinogenic to a variety of target tissues and animal species.[67]

Further support for this interpretation can be found in

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[66] Ibid, at 60-61.
[67] Appendix D.

the testimony of Drs. Nelson,[68] Preuss, [69] and Ms. Warren.[70]

o Reliance on Theories for the Carcinogentic Mechanism of Formaldehyde Which are at Variance with both the Weight of Scientific Opinion Generally and the Data on Formaldehyde

See previous discussion on pages 30-34 concerning the role of irritation as a causitive factor.

o Characterization of Federal Regulatory Policy on Action Levels for Federal Concern

In discussing action levels for federal concern, Dr. Todhunter states:

> In terms of individual lifetime cancer risks, the various federal agencies do not tend to regulate risks of $1X10^{-4}$ (1 in 10,000) and $1X10^{-5}$ (1 in 100,000). [71]

The testimony of the witnesses at the hearing, as well as others, flatly disputes Dr. Todhunter's statement. [72]

Apparently Dr. Todhunter had second thoughts about his position as well, since the following exchange with the minority counsel clearly contradicted his prior statement.

> MR. CLEMENT: ... I think the testimony by Dr. Arthur Upton yesterday was that he would be considerably concerned at risks in the magnitude of 1 times 10 to $^{-5}$ or 1 times 10 to $^{-6}$, down to 10 to $^{-4}$. Is that an area that you at EPA would also be willing to say that the agency should be concerned about?

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[68] Hearing Record, at 29.

[69] Ibid, at 91-92.

[70] Ibid, at 197.

[71] Appendix B, p.5.

[72] Hearing Record, at 77 (Crump), at 140 (Upton), and at 198 (Warren).

> DR. TODHUNTER: From 10 to -4 to 10 to -6 is an area where the agency normally gets anywhere from concerned and we had better have a look to see if there is anything happening, to an area where the agency would not show any particular concern. Many of the standard-setting practices of the agency, in fact, are targeted to about 10 to -5, and this happens in other agencies as well. OSHA, I believe, targets to around 10 to -4 or somewhat higher than that. It varies. [73]

Other examples of the lack of objectivity in the Todhunter memorandum include Dr. Todhunter's discussion on the need for site concordance,[74]

the emphasis on the lack of statistical significance of the results in the CIIT study at 5 ppm without noting the biological significance of the tumors observed,[75]

and the total absence of any discussion of the significance of so called benign tumors.[76]

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73 Ibid, at 152.

74 Compare the statement of Dr. Todhunter (Appendix B) with those of Dr. Gibson (Hearing Record at 243-244) and Dr. Nelson (Hearing Record at 22-23, 30, and 70-71).

75 Compare the statement on p. 7 in Todhunter Memorandum (Appendix B) with the statement made by Dr. Todhunter at the hearing. Hearing Record, at 153-154.

76 Ibid, at 63-64.

CONCLUSIONS

The science that supports a regulatory decision is frequently the subject of sharp debate. Given the limitations of scientific knowledge, we can do little more at this juncture than seek to safeguard the integrity of the process of developing, gathering, and interpreting data. In the case of EPA's formaldehyde decision, there were no open scientific debates -- either before or at the time of the decision -- and no impartial review of the decision. EPA needlessly left itself open to justifiable criticism that its decision is biased and in the words of Dr. Albert "was written in support of regulatory decision."[77]

The Subcommittee's recommendations, which are largely self-explanatory, are designed to address this problem by ensuring adequate public and peer review of the science used in agency decisions.

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[77] Ibid, at 36.

APPENDIX A

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SUMMARY OF HEARINGS TO REVIEW THE SCIENTIFIC BASIS OF THE ENVIRONMENTAL PROTECTION AGENCY'S CARCINOGENIC RISK ASSESSMENT ON FORMALDEHYDE

Prepared at the Request of the Subcommittee on Investigations and Oversight of the Committee on Science and Technology, U.S. House of Representatives

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BACKGROUND OF HEARING

In a memorandum dated February 10, 1982, Dr. John Todhunter, Assistant Administrator for Pesticides and Toxic Substances at the U.S. Environmental Protection Agency (EPA) recommended to Anne Gorsuch, Administrator of EPA, through Dr. John Hernandez, Deputy Administrator of EPA, that formaldehyde not be considered under section 4(f) of the Toxic Substances Control Act (TSCA). That document created major controversy because of the decisionmaking process used by EPA to arrive at their position, and by the potential impact on the health of formaldehyde workers and the general public, and on the economic health of the formaldehyde industry.

Approximately seven billion pounds of formaldehyde are produced annually ending up in a wide variety of products including carpeting, draperies, permanent press clothing, particleboard, paper bags, glued furniture, room deodorizers, cosmetics, shampoos and bath products, pesticides, and certain building insulation materials. The ubiquity of formaldehyde results in the exposure of virtually every American to the chemical. As such, the decision by EPA acquires tremendous importance.

Of perhaps greater importance is the decisionmaking process apparently used by EPA in arriving at their decision to not consider formaldehyde under section 4(f) of TSCA. The risk assessment underlying the decision appeared to depart from scientific principles for carcinogenic risk assessment, generally accepted principles developed over years through an iterative, international process incorporating peer and public review and input. Further, the decisionmaking process used by EPA appeared to have significantly excluded peer and

public review and input, and substantially discounted the massive body of literature demonstrating the carcinogenic power and potential of formaldehyde. Finally, allegations were made that the decisionmaking process used by EPA included the directed modification of scientific conclusions and the significant incorporation of non-peer-reviewed industry information. The potential importance of the EPA decision and decisionmaking process stems from their implications for future Federal policy on the regulation of carcinogenic substances.

In announcing the hearing, Representative Albert Gore, Jr., Chairman of the Subcommittee on Investigations and Oversight of the House Committee on Science and Technology, said, "The Subcommittee has a continuing interest in the development, evaluation, and use of scientific data by EPA and other Executive Branch agencies. (The purpose of the hearing was to) review the scientific principles used by EPA to assess the carcinogenic risk to humans from toxic substances and the process used by EPA to review scientific data. We are as much concerned with the rules for the formaldehyde risk assessment itself as we are about the precedent it may set for future agency risk assessments of potential carcinogens."

It was decided to have experts on the first panel present a scientific review of the EPA decision and decisionmaking process. The second panel of witnesses would present the analysis performed at the Consumer Product Safety Commission which had resulted in the Commission's banning of fut e installations of urea-formaldehyde foam insulation in residences and schools. The third panel would present the viewpoint of the EPA on the issue. A former EPA employee who resigned his position for reasons of conscience and two staff members from the Natural Resources Defense Council formed the fourth

panel. The Minority requested testimony from three specific witnesses. The request was granted, and these witnesses comprised the fifth and final panel.

The hearing was held on May 20, 1982.

REPORT SUMMARY

Briefly, this hearing brought out the following points:

1) The Todhunter memorandum to the EPA Administrator recommending against the consideration of formaldehyde under section 4(f) of TSCA had not been reviewed by the EPA staff nor by outside peer reviewers prior to its transmittal to the Administrator;

2) One ex-EPA employee testified that he had been ordered to incorporate verbatim changes in scientific information made by Dr. Todhunter, changes which were contrary to the scientific facts that the ex-employee had verified and forwarded;

3) Dr. Todhunter attended two EPA "science courts" on formaldehyde. The hearing also determined that these "science courts" were attended by representatives of the EPA the Formaldehyde Institute, two representatives of the National Academy of Sciences, but no representatives of other Federal agencies or public interest groups.

4) Witnesses associated with cancer research institutions, the Consumer Products Safety Commission, and a public interest group testified that the EPA's actions here regarding the nonconsideration of formaldehyde under section 4(f) of TSCA were procedurally improper, were in violation of the agency's statutory duty under section 4(f), were unsupported by scientific fact, were a serious departure from the major principles of established cancer policy, and were not in the public interest; and

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5) The EPA believes it needs exposure data before it can determine the existence of a "significant risk" under section 4(f) of TSCA, and therefore believes that its approach is reasonable, proper, and prudent.

WITNESS LIST

Thursday May 20, 1982 — 2318 Rayburn House Office Building

Panel 1
Scientific Review

Dr. Norton Nelson
Professor of Environmental Medicine
Institute of Environmental Medicine
New York University Medical Center

Dr. Roy Albert
Professor of Environmental Medicine
Deputy Director and Vice-Chairman of the Institute of Environmental Medicine
New York University Medical Center

Dr. Kenny Crump
President
Science Research System, Inc.

Dr. Richard Griesemer
Director, Biology Division
Oak Ridge National Laboratory

Panel 2
Consumer Product Safety Commission Perspective

Dr. Peter Preuss
Associate Executive Director, Health Sciences
U.S. Consumer Product Safety Commission

Dr. Andrew Ulsamer
U.S. Consumer Product Safety Commission

Dr. Murray Cohn
U.S. Consumer Product Safety Commission

Panel 3
U.S. Environmental Protection Agency Perspective

Dr. John Todhunter
Assistant Administrator for Pesticides and Toxic Substances
U.S. Environmental Protection Agency

Mr. William Petersen
Office of General Counsel
U.S. Environmental Protection Agency

Mr. Donald Clay
Director, Office of Toxic Substances
U.S. Environmental Protection Agency

Panel 4
Extra-governmental Viewpoints

Mr. Richard Dailey
Former employee, Environmental Protection Agency

Dr. Frederica Perera
Staff Scientist
Natural Resources Defense Council

Ms. Jacqueline Warren
Senior Staff Attorney
Natural Resources Defense Council

Panel 5
Witnesses Requested by the Minority

Dr. James Gibson
Vice-President and Director of Research
Chemical Industry Institute of Toxicology

Dr. Robert Sielken, Jr.
Texas A and M University

Dr. Sorell Schwartz
Professor of Pharmacology
Georgetown University

Members Present

Honorable Albert Gore, Jr., Chairman (D-Tenn.)

Honorable Bob Shamansky (D-Ohio)

Honorable Robert Walker (R-Pa.)

Note: All reference numbers refer to page numbers in transcript.

HEARING SUMMARY

STATEMENT OF MR. GORE

The hearing to review the scientific basis of the Environmental Protection Agency's carcinogenic risk assessment on formaldehyde was held on Thursday May 20, 1982 before the Subcommittee on Investigations and Oversight of the House Science and Technology Committee. Honorable Albert Gore, Jr. Chairman of the subcommitee, noted in his opening statement that the date of the hearing marked the first anniversary of the arrival of Anne Gorsuch as Administrator of the EPA. Mr. Gore highlighted the fact that the EPA has the statutory responsibility to protect the public health, yet has recommended massive budget cuts and has experienced staff reductions and losses of its most qualified scientists and staff morale.

Specifically under the provision of the Toxic Substances Control Act (TSCA) the "EPA must determine which chemicals should be regulated because they may present an unreasonable risk to public health and the environment." 1/

1/ p. 3.

With that mandate clearly stated, Mr. Gore proceeded to relate the facts of the ubiquity of formaldehyde citing the number of Americans exposed to the chemicals, and stressing the consequent importance of the EPA decision to not regulate formaldehyde under section 4(f) of TSCA.

Although he stressed the importance of the decision for that immediate reason, Mr. Gore quickly pointed out that the EPA position on formaldehyde

is far more important in "its implications for future Federal decisions on potential carcinogenics." 2/ The process by which the EPA arrived at their

2/ p. 4.

decision reportedly rejected principles for assessing the human risk from potential chemical carcinogens, principles which are widely accepted in the Federal and non-Federal community, and which are based on more than a decade of science and experience with peer and public review. These principles include a "positive bioassay result in a single species as evidence that the substance is a potential human carcinogen," 3/ the nonacceptance of "the

3/ p. 4.

idea of thesholds in making decisions about carcinogenic risks," 4/ and the

4/ p. 4.

belief that Federal agencies "should not wait for epidemiological evidence before taking action to limit human exposure to chemicals considered to be carcinogenic." 5/ Mr. Gore summarized the primary issue of the hearing this way:

5/ p. 4.

"Can an agency, without scientific support, without peer review, change the basic scientific presumptions on which all Federal environmental health laws have been based, presumption that requires, in the absence of scientific

certainty, that we follow a precautionary approach and protect the public from exposure to carcinogenic substances?" 6/

6/ p. 5.

A chronology of events related to the EPA decision was presented. The chronology began in the fall of 1979 when the Chemical Industry Institute of Toxicology (CIIT) informed EPA of some preliminary findings in its animal bioassay on formaldehyde. A panel of expert Federal scientists was convened by the National Toxicology Program for the Purpose of reviewing the CIIT study and analyzing it in relation to other literature on formaldehyde's carcinogenicity; this Federal panel concluded in November 1980 that formaldehyde was an animal carcinogen and should be presumed to be a human carcinogen. 7/ EPA

7/ p. 6.

viewed this finding as the trigger mechanism for regulatory action under section 4(f) of TSCA. The EPA staff recommendation for consideration of formaldehyde under section 4(f) was made in a priority review level one (PRL-1) document and presented to the Administrator of EPA by May 1981, approximately the time of Ms. Gorsuch's arrival.

In May 1981, Administrator Gorsuch asked Dr. John Hernandez, Deputy Administrator of EPA, to evaluate the evidence on formaldehyde. Dr. Hernandez convened three "science courts" in June, July, and August 1981; these meetings were not publicly announced, and were attended by members of EPA, lawyers and scientists of the Formaldehyde Institute (an association of formaldehyde

producers), two members of the National Academy of Sciences (NAS), and one representative from Oak Ridge National Laboratories (ORNL).

A memorandum from Donald Clay, 8/ director of the Office of Toxic

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8/ p. 7.

Substances (OTS), was sent in September of 1981 to John Todhunter recommending against the regulation of formaldehyde under section 4(f). Attached to the Clay memorandum was a paper based on the PRL-1, the Hernandez meetings, and other staff analysis, which analyzed the scientific and policy issues and detailed the staff opinions on them.

Mr. Gore continued citing the chronology of events, saying that the Technical Document which appeared in November 1981 was the PRL-1 after having been revised "under Dr. Todhunter's supervision and with his direct involvement. The Todhunter memorandum of February 10, 1982, was apparently not reviewed by the staff at the OTS." 9/

9/ p. 7.

The chronology was concluded by stating that the Todhunter memorandum contained much that had been rejected by the staff for inclusion in the Technical Document, but was presumably based upon the Technical Document and the Clay memorandum. The chronology as presented in the opening statement was as follows:

Fall 1979	CIIT notification of preliminary data to EPA.
	NTP convened panel of Federal scientists to review situation.
November 1980	Federal panel concludes that formaldehyde should be presumed to pose a carcinogenic risk to humans.
May 1981	EPA staff reviews data and recommendation reaches Administrator Gorsuch who asks John Hernandez to review.
June, July, August 1981	Three "science courts" with members of EPA, Formaldehyde Institute, NAS, and ORNL.
September 1981	Memorandum from Don Clay to John Todhunter recommending against 4(f), accompanied by options paper based on PRL-1, science courts, and other staff analyses.
November 1981	Technical Document appears (based on PRL-1, revised with supervision by John Todhunter).
February 1982	Memorandum to Anne Gorsuch from John Todhunter through John Hernandez recommending against 4(f).

Mr. Gore listed the central questions for the hearing in his opening statement:

(1) To what extent has Dr. Todhunter relied upon EPA's scientific staff and its Science Advisory Board in reaching the conclusions on the scientific evidence concerning formaldehyde?

(2) To what extent has EPA and Dr. Todhunter departed from the long-standing principles for carcinogenic risk assessment, and, given the wide acceptance of these principles, is there an accepted scientific basis for such departure?

(3) To the extent that neither the Technical Document nor the Clay memorandum agrees with Dr. Todhunter's decision document, what were Dr. Todhunter's sources of information?

(4) And to what extent did the EPA's decision receive peer review or public input? 10/

10/ p. 8.

Mr. Gore concluded his opening statement by stating,

> To the extent that EPA has departed from established scientific principles, the burden of proof rests on EPA to establish the scientfiic validity of its departure and to arrive at such a conclusion in a manner that preserves the integrity of the scientific process and the Federal decision-making process. 11/

11/ p. 8.

STATEMENT OF REPRESENTATIVE WALKER

The ranking minority member of the subcommittee protested the hearing on the grounds that the hearing was "an attempt to go completely beyond our committee jurisdiction and to interject this committee into the regulatory process at the Environmental Protection Agency." 12/

12/ p. 9.

Representative Walker commented that he was concerned that the hearing was the "result of the efforts of a few disloyal and disgruntled employees of the EPA . . ., faceless, nameless cowards . . . who have no loyalty and have no honor (and) are beneath contempt." 13/

13/ pp. 9-10.

Representative Walker then described the ubiquity of formaldehyde, even to its presence in every human body; as such, "the economic consequences of a ban on formaldehyde are enormous." 14/

14/ p. 11.

Turning to the carcinogenic potential of formaldehyde in humans, Representative Walker said that "my research of the literature for positive clues in this matter only turns up negative findings. . . . In fact, an American Cancer Society report in February of the year stated that there is no such proof." 15/ (That report was to be provided for the record.)

15/ p. 13.

It was Representative Walker's suspicion "that the average person cannot and will not tolerate more than four or five parts per million" 16/ of

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16/ p. 14.

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formaldehyde in air, with health reactions "such as drying of mucous membranes, headaches, coughing," 17/ and escape behavior occurring at those concentrations.

17/ p. 14.

Representative Walker continued by saying that certain studies indicate "that formaldehyde will cause cancer in rats if they are exposed to high levels of the chemical, 15 parts per million, for prolonged periods of time." 18/ His

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18/ p. 14.

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conclusion was that the "lack of positive data on human carcinogenicity leads me to think that there are some entry level plateaux to which most humans never reach, and that may also indicate that the actual risk to the general

population may be almost nonexistent." 19/ As such, Representative Walker

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19/ p. 14.

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maintained that under TSCA, the EPA must immediately regulate substances which pose a significant threat to the population, but formaldehyde did and does not pose such a threat and therefore did and does not require immediate regulation.

Representative Walker concluded his opening statement by reiterating his objection to the hearing on jurisdictional grounds.

Representative Gore responded that the counsel and chairman of the full committee had agreed on the appropriateness of the issue for the committee; a letter from the chairman of the full committee to the ranking minority member was to be provided for the record.

THE FIRST PANEL

STATEMENT OF DR. NORTON NELSON

Dr. Norton Nelson began his statement by reviewing his credentials and professional affiliations, including his current professorship of environmental medicine at the Institute of Environmental Medicine of the New York University Medical Center, and his prior directorship of that institute. Dr. Nelson's professional experience in the field extends for at least thirty years.

In those years, Dr. Nelson witnessed the "development of cancer research and cancer policy relating to environmental issues in this country." 20/ Dr. Nelson chose to "focus on the issue of principles for cancer control or cancer prevention." 21/ His basic message was clear:

> Current cancer policy, widely accepted throughout the world, from the Common Market to Japan--and I know these circles very, very well--to the United States of America, has been repeatedly expressed, and I think there is now a general consensus among most regulators and scientists throughout the world. Suddenly we seem to find ourselves in a situation in which this is perhaps quietly, perhaps accurately, but not publicly, being revised. 22/

20/ p. 20.

21/ p. 22.

22/ p. 22.

Dr. Nelson clearly stated that if review of the cancer policy shows the need, the policy should be changed, but "that such a review should be done under not merely internal auspices within Federal agencies of this country but should be subjected to external review and debate." 23/

23/ p. 22.

On the science of carcinogenicity, Dr. Nelson pointed out that:

> We now have . . . a remarkably solid basis of science for understanding the induction of cancer from external chemicals, and the induction of cancer from radiation. The problem of cancer is not as complicated scientifically as many would like to suggest that it is. Of course it is complex; of course it is difficult . . . . (S)cientific complexities should not be ballooned into a basis for paralysis or for inaction. . . . There is a strong parallelism between animal tests and human outcome. There is a strong parallelism between the . . . Ames test and human cancer. These are powerful tests, they have been used extensively, and they have received throughout the world a large body of confidence as predicters of potential human carcinogenicity. 24/

24/ p. 24.

A positive animal test does not invariably mean human carcinogenicity, it is here that the science of carcinogenicity, the proving of human carcinogencity, is a very difficult matter.

Epidemiological data does not necessarily prove a chemical's human carcinogenicity nor a chemical's safety. This is because "(e)pidemiological tools are crude; they are insensitive;" 25/ they require the careful following of many

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25/ p. 24.

subjects for many years. "Only the most violent and intense carcinogens are likely to be detected by epidemiological techniques as normally conducted." 26/

26/ p. 24.

Using lung cancer as his example, Dr. Nelson illustrated the crudeness of present-day epidemiological techniques by stating that a 5 to 10 percent increase in lung cancer over the current 100,000 lung cancer deaths each year would amount to a socially unacceptable risk of an additional 5,000 to 10,000 deaths each year and these additional deaths

> Would be almost undetectable by present-day epidemiological techniques. So we must be aware that the detection by epidemiological techniques is very, very crude, and this has led, quite simply, to the policy that we cannot wait for deaths and bodies accumulating before we have regulation. 27/

27/ p. 25.

Dr. Nelson then restated his basic message, that "it has been widely accepted throughout the world that animal studies plus additional evidence should signal a potential danger for man." 28/ Formaldehyde has been shown positively

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28/ p. 25.

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to cause cancer in animal tests in several different species, in several different strains, and at dose levels that are not far from those to which people are exposed. Formaldehyde is known to be an alkylating agent, reacting with

organic chemicals and DNA, the chemical blueprint of life forms, in a way known to be associated with carcinogens. Formaldehyde is genotoxic, producing changes in the genetic makeup of cells. Formaldehyde causes an increased incidence of malignant tumors in multiple species and strains, in multiple experiments, and to an unusual degree with regard to incidence, site and type of tumor, and age of onset; the meeting of these criteria provided sufficient evidence for the International Agency for the Research of Cancer (IARC) to label formaldehyde an animal carcinogen and to treat it as if it were a human carcinogen. Knowing these facts, it made no sense to Dr. Nelson to "re-review, re-review, re-review and wait until deaths occur, which are countable, some of which in fact may not be countable because they may be buried in this very large background of other sources of cancer." 29/ Rather, he clearly stated his position that "we go

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29/ p. 26.

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into some kind of control pattern now . . . control that is sufficient but not excessive . . . merited wholly on the basis of evidence that we have today." 30/

30/ p. 26.

Evidence available today involving cancers induced in test animals has elicited some discussion over the site of tumorigenesis; in test animals, nasal cancers have been most evident, yet nasal cancers have not been readily apparent in humans exposed to formaldehyde. Dr. Nelson addressed this by stating "that

one should not assume that total coincidence between animal tests and human outcome in the same organ are required. We have many examples in which the animal tests have predicted a severe danger of cancer, which is found in humans, but producing cancer in a different organ than that found in humans.

> Accordingly, what I find here is an alteration in the judgmental process by which in the last decade society has focused on the problems of cancer prevention through control procedures based on evidence which is generally and widely regarded as adequate to move in the direction of control. The alternative to wait until human evidence has accumulated is obviously irresponsible, insupportable, and inhumane. 31/

31/ p. 28.

Dr. Nelson concluded his statement by suggesting that any review of cancer policy be conducted publicly under competent control; he suggested the National Research Council of the National Academy of Sciences, the National Cancer Board, and the Board of Scientific Cancers of the National Toxicology Program as possible sites of review oversight.

STATEMENT OF DR. ROY ALBERT

Dr. Albert's short statement began with his reviewing of his professional involvement in the field of environmental cancer. Dr. Albert is a professor of environmental medicine at the New York University Medical Center, and is the deputy director and vice chairman of the Institute of Environmental Medicine. He was also the Deputy Assistant Administrator for Health and Ecology at the EPA from 1975 to 1976 where he was responsible for formulating the EPA's approach to carcinogen risk assessment; that program involved internal EPA

activity and "external participation by distinguished scientists from various parts of the country." 32/ Dr. Albert remains the chairman of EPA's Carcino-

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32/ p. 30.

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gen Assessment Group; the group performs "an agency-wide oversight role to assure the quality and consistency of the EPA's risk assessment." 33/

33/ p. 31.

Dr. Albert stated that the scientific review process had been "short-circuited," producing "all of the faults of" the Todhunter formaldehyde document. That document "was written in support of a regulatory decision. The exposition of science was clearly tailored to fit the decision. The document is far too one-sided to be regarded as a balanced assessment of the cancer risks from formaldehyde." 34/

34/ p. 32.

Dr. Albert placed the blame for this situation on the institutional requirements for review, and on the institutional structure for policy formulation. Specifically, Dr. Albert cited a serious gap in requirements for review: scientific documents developed in support of regulatory action must undergo elaborate review by in-house scientists and the Science Advisory Board, but there

are "no such review procedures for documents which are developed to support a decision not to regulate." 35/ On his second locus of blame, Dr. Albert commented that:

> It is only proper that political factors be taken into account in making regulatory decisions. . . . However, it is absolutely essential to the soundness of regulatory decisions that their underlying scientific assessments of health risks be shielded from the political forces that operate at the level of the regulatory offices. 36/

Dr. Albert's proposed plan to accomplish this objective was:

> One, to keep the responsibility for the scientific health risk assessments out of the regulatory offices in the EPA; and, two, to have all risk assessments, whether in support of regulatory action or regulatory inaction, be subject to rigorous scientific review by scientists within and outside the agency. 37/

Dr. Albert concluded his statement by commenting that "this is a simple, straightforward remedy to a chronic problem within the EPA that transcends personalities and administration." 38/

35/ p. 31.

36/ p. 32.

37/ p. 33.

38/ p. 33.

STATEMENT OF DR. KENNY CRUMP

Dr. Crump holds a doctorate in mathematics and has conducted and published research of statistical issues related to environmental data, dose response curves for carcinogens, and the assessment of human health risks using animal bioassay data or human epidemiological data. Dr. Crump has developed several statistical extrapolation procedures for estimating risks from low doses of carcinogens which use data gathered from much higher doses. The EPA has used one of these procedures, the "linearized multistage method," in conducting risk assessments for a number of carcinogens; without providing details of the procedures followed in performing their risk assessment, the Todhunter memorandum on formaldehyde states that the linearized multistage method was used.

Dr. Crump briefly explained that formaldehyde, a known mutagen, could be suspected of being a carcinogen which, at low doses, increases its carcinogenic potential in direct proportion to dose; as such, he noted the linearized multistage method, possessing this linear property at low doses, is an appropriate one for formaldehyde data.

Quite simply, when Dr. Crump applied his linearized multistage method to the data cited in the Todhunter memorandum, Dr. Crump was unable "to reproduce the risk estimates made in this document. When I used the assumptions that are described in the document, I got larger estimates of risk." 39/

39/ p. 38.

Dr. Crump concluded his statement by saying that, "using the methodology described in the Todhunter memorandum, . . . you would expect . . . about half

the people in the United States would have a risk (of developing cancer from exposure to formaldehyde) estimated . . . (as) greater than 1 in 10,000." 40/

40/ p. 40.

For the population of the United States, this amounts to an extra 20,000 cases of cancer.

STATEMENT OF DR. RICHARD GRIESEMER

Richard Griesemer holds doctoral degrees in pathology and veterinary medicine. He was a staff member of the National Cancer Institute, associate director of the Division of Cancer Cause and Prevention, and deputy director of the National Toxicology Program.

Dr. Griesemer reviewed four major studies of the carcinogenicity of formaldehyde. These four were conducted by: 1) the Federal Panel on Formaldehyde, 1980; 2) the American Cancer Society; 3) the International Agency for the Research of Cancer (IARC), October 1981; and 4) the IARC, February 1982. The conclusion reached in all these studies is that formaldehyde is an animal carcinogen and a carcinogenic risk to humans.

Dr. Griesemer then turned his comments "to some specific areas in the Todhunter memo which . . . might serve as examples for the kinds of comments scientists and the community might have offered to EPA if they had had that chance." 41/

41/ p. 42.

The Todhunter memorandum began with examples of usage of methods for evaluating chemical carcinogens, an opening which is not conventional in scientific methodology; "scientists would normally start . . . with definitions or with decision rules or criteria." 42/ Further:

42/ p. 43.

> The examples of usage that are given . . . were misleading, because formaldehyde was not the example used. Rather, it suggested strongly that a compound has to be carcinogenic in at least two species and in both sexes for the evidence to be sufficient. The sources cited from the IARC and a publication of mine are much more detailed and specific than that, and Dr. Nelson . . . referred to the criteria for sufficient evidence for carcinogenicity and formaldehyde meets all of those, and I think it would have been relatively straightforward just to have said so in the memorandum. 43/

43/ p. 43.

Dr. Griesemer verified that two strains of rats do develop nasal cancer when exposed to formaldehyde at 14 to 15 parts per million (ppm), but there is supporting evidence for the induction of nasal tumors at lower dose levels in the rat and mouse. There is also "evidence for mutagenicity and damage to the genetic apparatus of cells." 44/

44/ p. 43.

There is not, however, evidence for species specificity nor dependence upon route of exposure, i.e., he pointed out with current data it is unjustifiable to say that formaldehyde will cause cancers in only one or a few

species, and it is equally unjustifiable to say that cancers will occur only via certain specific routes of exposure. In the first case only the rat has been adequately tested, and in both cases the lack of adequate broad-based testing cannot be used as the justification for the definite statements that the carcinogenicity of formaldehyde is species-specific and dependent upon route of exposure.

Dr. Griesemer then commented upon the lack of evidence for cancers in other than rat nasal tissues;

> One of the possible confounding factors in making that evaluation is that in the rat studies so many of them died very early in life from nasal cancers--fatal cancers--that there were very few that might have been at risk to cancers in other parts of the body. 45/

45/ p. 45.

Further, there have been no data generated on responses to lower, less immediately fatal doses of formaldehyde. There are data stating that lesions formed not only in the lung and other parts of the respiratory tract, but also in the lachrymal gland. Finally on this point, Dr. Griesemer noted that humans are not obligate nose breathers, i.e., we can breathe through our mouths as well as noses, thereby putting humans at risk of formaldehyde-induced cancers in tissues other than nasal.

The reversibility of all of the adverse effects from formaldehyde exposure has not been proven. Regarding the CIIT study of reversibility, Dr. Griesemer stated that "the numbers of animals were very, very small and I do not think definitive conclusions can be drawn." 46/

46/ p. 47.

Dr. Griesemer then cited the scientifically incorrect use of "ulceration" in the Todhunter memorandum, an error of importance in the memorandum's treatment of cytotoxicity; the incorrect definition and use of "ulceration" allowed the development of an unproven mechanism (cytotoxicity developing into cancer) for chemical carcinogenicity used in the Todhunter memorandum.

Dr. Griesemer also took issue with the concept of a threshold for formaldehyde's carcinogenicity.

> So far as thresholds go, the only evidence I can find in any of the data is that formaldehyde does occur normally in the body at small amounts and for practical purposes that is a level below which we cannot reach. And so I suppose that makes it a threshold. Obviously, any additional exposures can be considered to increase the risk of cancer. 47/

47/ p. 49.

The Todhunter memorandum dealt only with malignant tumors, failing to deal with the incidence of benign tumors and the relationship and possible transition between benign and malignant.

Dr. Griesemer noted that formaldehyde is not only a complete carcinogen, i.e., it can induce cancers on its own, but it is also an initiator and promoter, thereby possibly adding to the carcinogenicity of other chemicals.

In summary, Dr. Griesemer stated that the Todhunter memorandum "understated the case for the carcinogenicity of formaldehyde and the significance of these findings for humans. . . . (T)he memorandum should be withdrawn and the subject reconsidered." 48/

48/ p. 51.

PANEL ONE--QUESTIONS AND RESPONSES

The responses to questions asked by Representatives Gore, Shamansky, and Walker of the first panel of witnesses highlighted six major points.

1) Americans are exposed to concentrations of formaldehyde which induce cancer in rats.

2) Science cannot determine a socially acceptable level of risk. Commenting as experts and not as scientists, there was agreement that 10^{-4} is an unacceptable level of risk for the general public, i.e., it is unacceptable to allow the general public to be exposed to a substance which will produce an additional cancer in every 10,000 persons nonoccupationally exposed. As stated in the Todhunter memorandum, half the population of the United States would be subject to a formaldehyde-induced malignant cancer risk of 1 in 10,000.

3) Current epidemiological techniques are crude and insensitive and would probably not be able to clearly indicate formaldehyde's carcinogenicity.

4) In the words of Dr. Nelson, the Todhunter memorandum:

> Is remarkable . . . in the sense that in each issue examined an extreme position is taken relating to the probable nonsignificance of the data on formaldehyde. It would perhaps be understandable for such an analysis to be prepared by industry or a manufacturing firm using formaldehyde. To be put forward as a dispassionate examination of evidence by a public agency responsible in this country for protecting the health of the public, this memorandum must be viewed as irresponsible. 49/

49/ p. 56.

In the words of Representative Shamansky, " . . . it looks as if the science of Dr. Todhunter has been prostituted . . ." 50/

50/ p. 57.

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5) According to the witnesses formaldehyde need not be banned, but should be controlled to reduce the risk of cancer in humans.

6) It was generally acknowledged that the mechanisms and details of the regulation of formaldehyde lay beyond the expertise of the panel and the jurisdiction of the subcommittee.

THE SECOND PANEL

STATEMENT OF DR. PETER PREUSS

Dr. Preuss is the associate executive director for health sciences at the Consumer Product Safety Commission. He was accompanied by Dr. Andrew Ulsamer and Dr. Murray Cohn, both also of the Consumer Product Safety Commission; neither presented testimony but did assist during the questioning period.

Dr. Preuss' concern about the potential chronic effects of formaldehyde are based on metabolism, mutagenicity, and carcinogenicity studies. The CPSC was concerned due to the ubiquitous nature of formaldehyde and the exposure of virtually every human to it; CPSC's most focused concern related to urea-formaldehyde (UF) foam insulation.

The analyses performed by the CPSC reached the following conclusions:

Presently, "the available epidemiological studies of humans exposed to formaldehyde vapor are inadequate to assess its carcinogenic potential." 51/

51/ p. 97.

The animal and chemical evidence clearly indicate that formaldehyde is an animal carcinogen and a presumed human carcinogen.

Further, formaldehyde may interact with other chemicals to prdouce cancer.

As such, the CPSC found it necessary to ban future residential and school installations of formaldehyde-emitting UF foam insulation in order to protect the public from unreasonable health risks.

Dr. Preuss made clear that the CPSC position was not based upon the worst-case scenio, and that the risk assessment performed by CPSC (which prompted the limited ban) may underestimate the total carcinogenic risk owing to the inclusion of only malignant cancer.

PANEL TWO--QUESTIONS AND RESPONSES

The questions asked by Representative Gore and by Mr. David Clement, Minority Technical Consultant, of the second panel highlighted three major points.

1) The panel of scientists from the CPSC accepted the positions of the witnesses on the first panel, especially on the issue of the insensitivity of present epidemiological studies.

2) The EPA had not consulted with the CPSC prior to developing the recommendation made in the Todhunter memorandum.

3) Being familiar with the Todhunter memorandum, in the words of Dr. Preuss, "there is not anything in that memorandum that would have caused me to change my recommendation as a scientist to the Commission." 52/

52/ p. 102.

THE THIRD PANEL

STATEMENT OF DR. JOHN TODHUNTER

Dr. Todhunter is the Assistant Administrator for pesticides and toxic substances at the EPA. He was accompanied by Mr. Donald Clay, Director of the Office of Toxic Substances, and Mr. William Peterson, of the Office of General Counsel, both also of the EPA; neither presented testimony but did assist during the questioning period.

Dr. Todhunter's testimony focused on three major issues.

He wished to clarify the fact that the EPA under the last Administration did not propose to regulate formaldehyde. Under the present EPA, there is the need to demonstrate significant risk prior to considering a substance under section 4(f) of TSCA, and there is the need for exposure data prior to determining if there is a significant risk.

Dr. Todhunter also sought to clarify the situation regarding the present EPA and risk assessment; "the second misconception is that EPA has somehow departed from longstanding principles of risk assessment in developing its position on formaldehyde. . . . The question is whether or not the cancer risk is significant." 53/ The position at EPA is that formaldehyde's cancer risk

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53/ pp. 121-122.

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to humans at present is not significant enough to warrant consideration under section 4(f) of TSCA, lacking sufficient exposure data to support the claim of significant risk.

Finally, Dr. Todhunter wished to demonstrate that the unanimity in science policy on carcinogen research and regulation discussed by previous witnesses was actually less than unanimous. Dr. Todhunter read selected excerpts from two sources to support his contention. From the Federal Report on Formaldehyde, he read a passage saying that "it is conceivable that the cytotoxic effects of formaldehyde may play a part in its overall carcinogenicity." 54/

54/ p. 126.

From a report by a special study group of the American Medical Association published in the July 17, 1981, Journal of the American Medical Association, Dr. Todhunter read that:

> Carcinogenicity in animal tests does not per se predict either risk or outcome in the human experience. Moreover, an agent can metabolize differently in diverse species and even strains of mice. Thus, a substance can be carcinogenic for certain organs in one species but relatively harmless in other organs or in other species.' Furthermore, in the same report it states 'there is some evidence from both experimental animals and man that there is a threshold for many carcinogens. Thus the concept of a threshold level beneath which exposure is harmless cannot be rejected.' I just add that to indicate that I do not think it is by far unanimous that there is only one way to look at tumor data. 55/

55/ p. 130.

Dr. Todhunter concluded his statement by saying that "EPA believes that the approach which is being taken is reasonable, proper, and prudent." 56/

56/ p. 130.

PANEL THREE--QUESTIONS AND RESPONSES

The questioning of Dr. Todhunter, Mr Clay, and Mr. Peterson by Representatives Gore and Walker, and by Mr. Clement, highlighted six major issues.

1) Dr. Todhunter read selected excerpts from several sources, none of which had been provided for review and about which Representative Gore commented "the problem that we have is that in taking it out of its context without any ability for us to review other parts of the document. That is the only problem." 57/

57/ p. 127.

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2) Dr. Todhunter denied that the Formaldehyde Institute or the industry had undue influence on the EPA decisionmaking process. However, the record was unclear regarding the amount and timing of information exchanged between Dr. Todhunter and Mr. John Byington, "strategic counsel" of the Formaldehyde Institute. 58/

58/ p. 137.

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3) Dr. Todhunter stated that he had a limited role in revising the decision document, and had nothing to do with revising the PRL-1. 59/

59/ pp. 135-136.

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4) It was clearly brought out that the Todhunter memorandum was not reviewed by the EPA staff nor by outside peer reviewers prior to the transmittal of the document to the Administrator. It was also clear that, in the words of Dr. Todhunter, the document "was not written primarily as a scientific document." 60/

60/ pp. 146 and 170.

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5) As presented in Dr. Todhunter's testimony and responses to questions, the EPA maintains that it needs human exposure data in order to justify a determination of significant risk, that "we have always said we need to go back and get better exposure numbers to be sure if that is correct, to see if that is in fact what is there." 61/

61/ p. 160.

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6) In response to questions, Dr. Todhunter made it very clear that he does not "believe that positive epidemiological data is needed before regulation of a chemical carcinogen is warranted." 62/

62/ p. 186.

THE FOURTH PANEL

STATEMENT OF MR. RICHARD DAILEY

Richard Dailey holds a bachelor of science degree in the fields of biology and chemistry, and has studied environmental science, oncology, and toxicology at the graduate level. For about two and one-half years, until early 1982, Mr. Dailey had been an employee of the EPA "handling the agency's formaldehyde efforts." 63/ His responsibilities included the analysis,

63/ p. 205.

interpretation, and synthesis of scientific information made available to him, and the transmittal to management of accurate, succinct reports on chemicals undergoing review. His job was, "for want of a better word, to be a generalist." 64/

64/ p. 204.

Mr. Dailey presented a chronology of events related to formaldehyde and the EPA; his chronology was identical to that presented in the opening statement by Represenative Gore, with the exception of providing greater detail from an eyewitness perspective.

Mr. Dailey recounted how in October 1981 he had been "given a copy of the PRL-1 with changes to be made that had been penciled in by Dr. Todhunter. (He) questioned some of the changes that were to be made but was ordered to

incorporate Dr. Todhunter's comments verbatim." 65/ Mr. Dailey provided

65/ p. 211.

one example to illustrate his situation.

Simply stated, the issue involved the quantity of free or unassociated formaldehyde in a human body. Dr. Todhunter cited a study as the source of his figure of three parts per million (ppm) of free or unassociated formaldehyde in a body, "a threshold below which one would not expect cancer induction." 66/ Mr. Dailey contacted the author of the study and learned

66/ p. 212.

from the author that "at least 90 percent" 67/ of the endogenous 3 ppm

67/ p. 213.

of formaldehyde would not be free or unassociated but would be bound and unavailable for reactions, including carcinogenic ones. Further, Mr. Dailey noted he had been ordered not to use data in preparing technical documents which had "not received traditional peer review." 68/ Mr. Dailey learned

68/ p. 212.

from the author of the study cited by Dr. Todhunter that the study had not been published, "was not even in proper form to be sent to a journal for consideration," 69/ and that no one at the EPA "was in receipt of any

69/ p. 212.

personal communication from him stating the results of his findings." 70/

70/ pp. 212-213.

Because the data had not been traditionally peer reviewed nor published, and because the number cited by Dr. Todhunter was simply in error, Mr. Dailey "felt at that time that I could not in good conscience and without compromising my own integrity make the requested changes." 71/ Later, Mr.

71/ p. 213.

Dailey received a copy of the Technical Document:

> With handwritten comments from Dr. Todhunter ordering more changes. It was at this point that I tendered my resignation. I believe that it is the responsibility of a Government employee to carry out the objectives of his respective agency to the best of his ability, regardless of his personal position on those objectives. However, I also believe that when objectives and means of obtaining those objectives become so untenable as to compromise the quality of one's work and integrity, it is one's responsibility to resign that position, and that is what I have done. 72/

72/ p. 214.

STATEMENT OF DR. FREDERICA PERERA

Frederica Perera holds a doctorate in public health and is a senior staff scientists with the Natural Resources Defense Council (NRDC).

Dr. Perera's statement began by recounting the ubiquity of formaldehyde, and the finding that people in some workplace and home environments encounter levels of formaldehyde "comparable to those that cause tumors in animals." 73/

73/ p. 216.

Moreover, Dr. Perera emphasized that there is wide-based support in the scientific community of the position that "formaldehyde gas should be considered 'for practical purposes' as if it represented a risk of cancer to humans." 74/

74/ p. 216.

Dr. Perera listed the areas in which Dr. Todhunter's memorandum was "in sharp contrast with the . . . judgments of experts in carcinogenesis." 75/

75/ p. 217.

These areas were: a) "formaldehyde is a potential human carcinogen," 76/

76/ p. 217.

b) formaldehyde's carcinogenicity displays "'species specificity'," 77/

77/ p. 217.

c) the carcinogenicity of formaldehyde shows "'a strong dependence on route of exposure'," 78/ d) "formaldehyde produces tumors via an indirect mechanism

78/ p. 217.

of action," 79/ and e) "there is probably a threshold for the carcinogenic

79/ p. 217.

effect." 80/

80/ p. 217.

On the issue of epidemiological data, Dr. Perera noted that the insensitive studies conducted to date are "'inadequate' to evaluate the carcinogenic effect (of exposure to formaldehyde) in human populations," 81/ but that

81/ p. 218.

epidemiologic studies presently underway "suggest an increased risk of cancer at different sites in workers," 82/ and may in time, "if confirmed, . . . provide evidence of an association" 83/ between formaldehyde exposure and cancer.

82/ p. 218.

83/ p. 218.

The "principles for assessing carcinogenic risk that have been widely accepted by the scientific community for over a decade" 84/ were described in detail by Dr. Perera. These are: a) "animal testing data from properly designed and well conducted tests are adequate for concluding that a chemical substance or agent is a likely carcinogen in humans," 85/ b) it is not currently possible using available methods to extrapolate from animal data a safe population threshold for any carcinogen, regardless of the mechanism

84/ p. 219.

85/ p. 219.

of action," 86/ and c) "positive human data are not necessary to regard an

86/ pp. 219-220.

agent as a likely human carcinogen warranting protective action." 87/

87/ p. 220.

Dr. Perera's and the NRDC's position was clear.

> EPA's decision not to make formaldehyde a priority for regulatory assessment on the basis of the arguments presented in the Todhunter memo could effectively rewrite the agency's cancer policy. The result would be a significant relaxation of public health protection from cancer-causing substances. We believe that there is a consensus in the scientific community that there are no new data which would justify such a serious departure from the major principles of established cancer policy. 88/

88/ p. 220.

STATEMENT OF MS. JACQUELIN WARREN

Ms. Warren is a senior staff attorney at the NRDC. A relatively small part of Ms. Warren's statement dealt with the EPA's new interpretations of data in arriving at their decision not to consider formaldehyde under section 4(f) of TSCA. Ms. Warren briefly emphasized that the EPA's decisionmaking assumptions "depart radically from accepted principles of cancer risk assessment, 89/ and

89/ p. 227.

"lack a sound scientific basis." 90/

90/ p. 227.

Ms. Warren focused most of her statement on the legal aspects of the EPA's action. The witness pointed out that section 4(f) of TSCA "is not a regulatory vehicle, (but) it is a priority setting mechanism. . . . It was Congress' way of bringing to EPA's attention those chemicals which posed a risk of cancer, genetic mutations, or birth defects, so that they could have a higher priority for assessment and possible regulatory action than the myriad of other chemicals that EPA could address under TSCA." 91/

91/ p. 222.

After a reasoned argument validating this interpretation of section 4(f), Ms. Warren quoted from Mr. Donald Clay's September 11, 1981, memorandum recommending to Dr. Todhunter not to consider formaldehyde under section 4(f), but to reserve 4(f) for "addressing those 'situations that require a crash effort to remedy a very serious hazard to public health'." 92/ Ms. Warren commented

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92/ p. 226.

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that the

> Basic congressional intent to require EPA on an expedited basis to take a closer look at chemicals that cause the most serious adverse effects in laboratory studies and for which there appears to be widespread exposure, has been completely frustrated. Apparently EPA is willing to take a second look only when a ''very serious hazard to public health'' has already been demonstrated. 93/

93/ p. 226.

Because the EPA is not fulfilling the purpose of section 4(f), Ms. Warren stated that NRDC would very shortly be engaged in litigation on the matter.

In the NRDC viewpoint, "EPA has engaged in a series of actions that we consider procedurally improper, violative of the agency's statutory duty under section 4(f) of TSCA, and not in the public interest." 94/

94/ p. 228.

PANEL FOUR--QUESTIONS AND RESPONSES

The responses to questions asked by Representatives Gore and Clement highlighted certain points in the statements of Mr. Daily, Dr. Perera, and Ms. Warren.

Mr. Dailey emphasized that there were no representatives of public interest groups nor representatives of other Federal agencies present at the "science courts" on formaldehyde held by Dr. Hernandez of the EPA.

Dr. Perera's responses clarified that a set of data, when subjected to direct statistical analysis, may lack statistical significance, but can be biologically significant owing to the rarity of the physiologic phenomenon measured. In the case of formaldehyde and the extreme rarity of the observed nasal tumors in test animals, if the biological significance of the rare tumors is considered, it is possible to conclude that "you do have statistical significance" 95/ with those data.

95/ p. 229.

Finally, statements made during the questioning period emphasized that "'there is no recognized method as yet for determining the existence of a threshold for a carcinogen in the human population'" 96/ and

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96/ p. 242.

'It is generally accepted that a population threshold which would define a risk-free dose for a group of people composed of diverse individuals if it exists, cannot now be demonstrated. Federal agencies do not accept the idea of thresholds in making decisions about carcinogenic risks.' 97/

97/ p. 242.

THE FIFTH PANEL

STATEMENT OF DR. JAMES GIBSON

James Gibson holds a doctorate degree in pharmacology and is Vice President and director of research for the Chemical Industry Institute of Toxicology, "a nonprofit, independent public institution . . . engaged in testing, research, and training in toxicology, . . . financially supported by the industry." 98/

98/ p. 255.

Dr. Gibson provided laboratory results to support the statement that "both the time of tumor development as well as the sensitivity to tumor formation for formaldehyde was species- and dose-dependent." 99/

99/ p. 257.

Extending the concept of variable species sensitivity, Dr. Gibson spoke of the possible influence on formaldehyde toxicity by respiratory tract mucus; the "mucus may provide protection of respiratory epithelial cells at low concentrations of formaldehyde exposure, a protective mechanism lost at high formaldehyde concentration." 100/

100/ p. 258.

Dr. Gibson offered possible chemical transformation schemes for formaldehyde in a body, including "damage to DNA and/or cell death." 101/

101/ p. 260.

The concept of "'effective dose'" 102/ was mentioned in the witness'

102/ p. 261.

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statement. This concept "involves the measurement of the dose of formaldehyde reaching the nasal epithelium;" 103/ the dose reaching that target can vary

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103/ p. 260.

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across species due to different reflexive respiratory rate changes, i.e., species which by reflex action decrease the rate of respiration more than another species will, given the same concentration of formaldehyde in air, receive a smaller "effective dose" at the target organ or tissue. Dr. Gibson suggested that "the expression of formaldehyde dose should be as an 'effective dose' rather than as a concentration in air." 104/

104/ p. 261.

Dr. Gibson noted that formaldehyde has been observed under some conditions to be mutagenic in some cells, but not mutagenic under other test conditions. The witness also spoke of the variable carcinogenicity of formaldehyde, an effect which may be variable owing to variable DNA repair rates. Dr. Gibson

also wished to stress that "the results of various genetic toxicity studies are mixed; some are positive and some are not." 105/

105/ p. 262.

On the topic of risk assessment, Dr. Gibson said that "risk assessment across species, as from rat to mouse or to humans, is in most cases an extremely inexact procedure." 106/

106/ p. 264.

Dr. Gibson concluded his statement by saying,

> Low-dose extrapolation by CIIT of the CIIT rat and mouse data for the purpose of human risk assessment must await additional knowledge on our part of the mechanism of formaldehyde's effects. Specific information on endogenous concentrations of formaldehyde in human tissues, cytological effects, occupational health effects, and mortality experience in humans must also be collected to fully understand formaldehyde's potential carcinogenesis in humans. The significance of the carcinogenic effects in rats, however, dictates that formaldehyde should be kept at the lowest possible concentration in the workplace, in homes, and in ambient air. 107/

107/ pp. 264-265.

STATEMENT OF DR. ROBERT SIELKEN, JR.

Robert Sielken is a statistician with Texas A and M University, and has been a consultant to the Formaldehyde Institute, the EPA, and the Food and Drug Administration. Dr. Sielken presented some slides but did not have a written statement. Parts of his testimony had been presented at the EPA "science courts" on formaldehyde. The work that he spoke of in this hearing had neither been peer reviewed nor published.

Dr. Sielken's work involves the development of computer software and the providing of the statistical background for models incorporating the time to a carcinogenic response into risk assessment, i.e., how "exposure time, the length at which an animal or a man would be subject to risk, . . . might be included in the risk assessment." 108/

108/ p. 268.

Dr. Sielken noted some limitations of various statistical models and procedures for low dose risk extrapolation. In particular, Dr. Sielken commented on the risk assessment used to support the CPSC's limited ban of urea formaldehyde foam insulation (UFFI). In his view, "the cancer risk due to inhalation of formaldehyde released from UFFI is probably at least 100 times smaller than the quoted 51 in 1 million." 109/

109/ p. 273.

STATEMENT OF DR. SORELL SCHWARTZ

Sorell Schwartz is a professor of pharmacology at Georgetown University.

Dr. Schwartz began his testimony by stating that formaldehyde "is in fact demonstrated to be an animal carcinogen, and my own personal philosophy is that if something is demonstrated to be an animal carcinogen, irrespective of all theoretical considerations, it must be, at this particular time, for reasons of prudence, to be considered as a human carcinogen." 110/

110/ p. 274.

Dr. Schwartz continued "that it is not the responsibility of the scientist to determine the acceptability of the risk. It is a political responsibility." 111/

111/ p. 275.

Dr. Schwartz concluded by saying, "I believe in the final analysis . . . the Todhunter memo dealt with not the level of risk, but the acceptability of that risk under 4(f) at that particular time." 112/

112/ p. 280.

PANEL FIVE--QUESTIONS AND RESPONSES

The responses to the questions asked by Representative Gore and Mr. Clement clarified several points in the statements of Drs. Gibson, Sielken, and Schwartz.

All three witnesses had been requested by the minority with very short lead-time. Only Dr. Gibson had a written statement. None of the witnesses' statements or appearances was paid for by the Formaldehyde Institute. Only Dr. Sielken had been a consultant to the Formaldehyde Institute.

Dr. Schwartz clarified his position on the Todhunter memorandum by saying that "I have never read anything in the Todhunter memo which to me involves science." 113/ Dr. Schwartz then listed the scientific judgments in the

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113/ p. 283.

Todhunter memorandum that he disagreed with. These were: 1) the emphasis on risk assessment information; 2) the focus on epidemiology. "I do not favor the idea that negative epidemiologic data signifies negative human effect. You cannot prove a negative"; 114/ and 3) that rat nasal cancers were probably

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114/ p. 283.

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caused by irritation. "I think it is another view but I would not accept it as a fact." 115/

115/ p. 285.

Dr. Gibson clearly stated that cancers from formaldehyde exposure should be looked for not only in humans' upper nasal areas, but also in tracheal tissues, mouth, larynx, throat, and maybe lung, if the formaldehyde adhered to a foreign body and was carried into the lung.

Dr. Sielken made clear that the use of median exposures in the Todhunter memorandum may over or underestimate the real risk of cancer from formaldehyde exposure.

Dr. Sielken also clarified his position on acceptable risk and exposure levels. Dr. Sielken said that he does not consider a lifetime exposure level of 1 ppm "as being acceptable to me." 116/ Representative Gore pointed out

116/ p. 301.

that the "OSHA level is 3 (ppm)." 117/ Dr. Sielken responded "that is

117/ p. 301.

occupational exposure. . . . I am talking about a 24 hour-a-day, 7 day-a-week exposure. On the other hand, based on the studies of the CIIT, I think the OSHA standard probably needs reexamination." 118/

118/ p. 301.

- APPENDIX B

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

FEB 10 1982

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of Data Available to the Administrator Concerning Formaldehyde and di(2-ethylhexyl) Phthalate (DEHP)

FROM: John A. Todhunter, Ph.D.
Assistant Administrator
for Pesticides and Toxic Substances (TS-788)

TO: Anne M. Gorsuch
The Administrator (A-100)

THRU: John W. Hernandez, Ph.D.
Deputy Administrator (A-101)

Summary

At your direction I have reviewed the materials prepared by the Office of Toxic Substances in regard to formaldehyde and DEHP. I have also reviewed the materials prepared early in 1981 by OTS which were appended to a letter from NRDC, dated September 4, 1981. This memorandum is a statement of my professional conclusions and policy recommendations regarding the documents reviewed. In summary: I find that I concur with the current recommendations of OTS that formaldehyde and DEHP ought not be considered under section 4(f) and that the preliminary drafts relied on by NRDC in their letter to you were incomplete and flawed.

Technical and Policy Issues Related to Section 4(f)

The Toxic Substances Control Act (TSCA) was enacted by Congress to protect human beings and the environment from those chemical substances and mixtures whose manufacture, processing, distribution in commerce, use, or disposal pose unreasonable risks of injury. One of the provisions of the Act is Section 4(f), which states that:

> Upon receipt of 1) any test data required to be submitted under this Act, or 2) any other information available to the Administrator, which indicates to the Administrator that there may be a reasonable basis to conclude that a chemical substance or mixture presents or will present a significant

> risk of serious or widespread harm to human beings from cancer, gene mutations, or birth defects, the Administrator shall, within the 180-day period beginning on the date of the receipt of such data or information, initiate appropriate action under section 5, 6, or 7 to prevent or reduce to a sufficient extent such risk or publish in the FEDERAL REGISTER a finding that such risk is not unreasonable. For good cause shown the Administrator may extend such period for an additional period of not more than 90 days. The Administrator shall publish in the FEDERAL REGISTER notice of any such extension and the reasons therefor.

The purpose of section 4(f) is to identify certain chemical substances or mixtures as high priority candidates for regulatory action and establish a deadline for acting to regulate such substances as are found to meet section 4(f) criteria. A chemical could meet the section 4(f) criteria when there may be a reasonable basis to conclude that it presents a risk from one of three effects--cancer, gene mutations or birth defects, and that the risk of this effect is significant and either serious or widespread. None of these terms--significant, serious or widespread--is precisely defined in TSCA.

The common technical use of these terms in the bio-medical sciences would suggest that "significant" would address both the probability that a risk of any magnitude could occur as well as the magnitude of the risk; and that "serious" and "widespread" would address the nature (i.e., major vs. minor) of any harm resulting and the size of the affected population, respectively.

For purposes of illustration, the following examples of usage are possible:

"Significant" -

> A particular animal cancer bio-assay indicates that chemical compound X is a carcinogen in at least two species tested and all sexes in these species. Compound X generally may present a risk of being a human carcinogen. To be "significant" it should further be established that--at human exposure levels--the risk is probable and would be high. A different chemical, compound Y, is positive in one species, one sex and at one high dose. It could, in theory, be a human carcinogen but it need not generally be considered to pose a "significant" risk to humans based solely on the one positive finding. Strong evidence for human risk should generally require that the carcinogenic effect be established as active in more than one species or at more than one dose.

If for compound X above, it were found that the carcinogenic effect is due to activation of a metabolic pathway not found in humans, then the risk from compound X could be deemed not "significant" as it would not occur in humans.

The carcinogenic effects of compound X could also be found to be secondary to physiological events (deposition of microcallculi, hormonal changes, necrosis, etc.) triggered by compound X at levels used in bio-assays but not at levels to which humans are exposed. Compound X would probably not pose a "significant" risk to humans. (See footnote 1)

"Serious" -

The concept of "serious" harm would have more utility in the consideration of gene mutational events or birth defects than in the case of cancer since malignant neoplasms in general are serious. Section 4(f) also draws a distinction between benign and malignant growths by use of the term "cancer" rather than "tumors".

"Widespread" -

A teratogen could produce a minor anomaly. If this occurred at one in one hundred thousand births, it need not be necessarily "serious" or "widespread". The same outcome at one in one hundred births, however, would certainly be "widespread".

The determination that a chemical meets the criteria of section 4(f) is, by statute, made by the Administrator of EPA.

When a chemical meets the criteria for section 4(f) priority status, the Agency must decide quickly whether to initiate action. The provision states that the Administrator must, within 180 days of the Administrator's receipt of the information

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(1) These considerations as to weight of evidence to establish human risk generally follow the recognized International Agency for Research on Cancer (IARC) criteria (IARC, Internal Technical Report No. 78/003) as to whether evidence is negative, limited, or sufficient for human carcinogenicity as well as the amplification of these criteria presented by Griesemer and Cueto (Scientific Publication No. 27, IARC, Lyon; p. 259-281 (1980)). The second paragraph draws from Weisburger and Williams (in Toxicology, Casarett and Doull, Eds., 2nd edition, MacMillan, N. Y. (1981) as well as from a more recent paper of Squire (Science, 214; 877-880 (1981)).

indicating the risk, initiate appropriate action under section 5, 6, or 7 of TSCA, or explain in the FEDERAL REGISTER why the risk is not unreasonable. As a purely technical matter, only rarely would a single study provide a reasonable basis to conclude that a chemical presented or would present a significant human risk. Risk is a function of toxicity and exposure. Therefore, exposure evaluations (which generally must rely on other studies than those raising toxicological concerns) are required in order to properly quantitate risk. The probability that risk would indeed occur can in general, likewise, only be assessed by review of all the available literature on a given chemical. Only when the diverse pieces of information which must go into a proper risk assessment are assembled into a reasoned evaluation can there generally be any scientific basis on which to draw reasonable conclusions as to the nature of human risk posed by a given chemical.

In certain instances the available data on a chemical may suggest that it poses a human risk but be insufficient to reasonably support a conclusion that the chemical presents a significant risk of serious or widespread harm [i.e., similar to a section 4(f) determination] and/or an unreasonable risk [a determination called for in other parts of TSCA]. The distinction between chemicals which may pose a human risk and those which pose either a significant and/or unreasonable risk [applicable to section 4(f) and/or section 5, 6, or 7, respectively] is important from a policy standpoint. This distinction and the TSCA data collection authorities allow the Agency to deal with chemicals on which the data are suggestive but inconclusive by use of sections 4(a), 5(e), and/or 8 so as to better develop a data base. This distinction also allows the Agency to place less priority on such substances as may be found to pose less than significant human risk even though the Agency may want to retain some oversight of activities involving such a substance.

Applicability of TSCA Section 4(f):

The principle decision before the Administrator at present is whether or not the data available on formaldehyde meet the criteria set out in section 4(f) of TSCA. The technical and policy arguments that these criteria are not met are presented for each substance in this report in greater detail below. Legal conclusions as to section 4(f) are not within my realm of expertise. In this report I have tried to define the technical practicalities of section 4(f) and to address the relevant policy issues.

Generally, the approach to section 4(f) that is presented is that, until the Administrator has reviewed the available data and reached a conclusion as to the significance of risk, any designation of data as having triggered section 4(f) is

scientifically arbitrary. This has tremendous practical and scientific underpinings as, in general, no one study by itself will be sufficient to indicate "significant" risk and the required determination that "there may be a reasonable basis to conclude that a chemical substance or mixture presents or will present a significant risk . . . " should, therefore, require a synthesis of existing and newly developed knowledge. Only when this synthesis is accomplished can a reasoned conclusion, in general, be reached.

As a policy matter, it is recommended that risk situations which are "significant" in the context of priority setting via section 4(f) be clearly distinct from risk situations which are generally not of immediate regulatory interest. In terms of individual lifetime cancer risks, the various federal agencies do not tend to regulate risks of 1×10^{-5} or lower and tend to be ambivalent about risks between 1×10^{-4} - 1×10^{-5}. Certainly (as absolute risks) these risk levels could never be detected any normal way and would (using 1×10^{-4} as an upper bound) represent increments of 0.03% or less above the estimated individual risk of persons in the U.S. population as a whole. (This risk is 1 in 3 or 3.3×10^{-1} according to the most recent National Cancer Institute figures.) In CPTS the relative risk range of 1×10^{-4} to 1×10^{-6} or lower has been a low concern range in general. The use of a range is appropriate since these risks, even at the 95% upper confidence limit, are only relative estimates for specific chemicals. To use such risk estimates as absolutes is inappropriate. This point was recently emphasized by Dr. David Rall, Director of the National Toxicology Program, in testimony before Rep. Gore during the 1981 NTP appropriations hearings.

FORMALDEHYDE:

Summary

Technical and policy discussion of these points is to be found in the body of this report.

Conclusions With Respect to Formaldehyde:

I concur with the recommendations of OTS staff that formaldehyde does not meet the criteria of section 4(f) for the following reasons:

(A) There is suggestive evidence that there may be human exposure situations--based on the integrated animal data base--which may not present carcinogenic risk which is of significance.

(B) There is a limited but suggestive epidemiological base which supports the notion that any human problems with formaldehyde carcinogenicity may be of low incidence or undetectable. It would not appear reasonable to say that a significant risk situation exists from these data.

(C) Assuming that risk--of some magnitude--does exist the calculated relative risks tend to fall into ranges which normally are of from low priority to no concern such as those discussed in the section immediately above on the applicability of TSCA section 4(f).

(D) One can, therefore (and as amplified below) conclude on the basis of available toxicological data, exposure information, and risk analysis techniques that: (a) formaldehyde is a carcinogen in the rat by the inhalation route; (b) its carcinogenic potential appears to vary significantly with species and route; (c) under certain exposure conditions it could present some carcinogenic risk to humans; and (d) given available data the risk estimates suggest that certain populations may experience a carcinogenic risk--albeit low--due to formaldehyde exposure. However, because of the nature of the toxicology data and the unreliability in the exposure data one cannot reasonably conclude, at this time, that formaldehyde poses a significant risk among the U.S. population.

Interpretation of Animal Studies with Respect to Human Risk -- Of a variety of bioassays (Table I) done since 1954 to assess the carcinogenic potential of formaldehyde only two have given clear positive results attributable to formaldehyde: a Chemical Industry Institute of Toxicology Study (CIIT) reported in preliminary form by Swenberg et al, Cancer Research, 40, 3398 (1980) and a study underway at the New York University Medical Center which is an extension of an earlier New York University study of 1979. Both of these have been inhalation studies in the rat. The CIIT study used three dose levels plus a control, the New York University study used a single high dose equivalent to the highest CIIT dose. Only nasal carcinomas were found in either study. Approximate mean lifetime incidences were 0% in control rats; 0% in rats at 2.1 ppm formaldehyde; 1.9% in rats at 5.6 ppm (not statistically significant); and 50% in rats at 14.1 ppm in the Swenberg study. The New York University study indicates (by letter of August 17, 1981 from Dr. Arthur Upton) an incidence of about 10% in rats at 14 ppm of formaldehyde.

Table I: Studies Considered in Evaluating the Carcinogenic Potential of Formaldehyde

Species	Route	Dose	Length	Incidence	Reference
Rat, ♀ & ♂, Fischer 344	inhal.	0, ppm 2.1 ppm 5.6 ppm 14.1 ppm	24 mos.	(0%) (0%) (1.9%) (50%)	CIIT study of Swenberg et al, nasal tumors only
Rat, ♂ Sprague-Dawley	inhal.	14 ppm	lifetime (19 mos. completed)	(~10%) nasal tumors	On going NYU study reported by Upton letter of Aug. 17, 1981
Rat, ♂, Sprague-Dawley	inhal.	14 ppm+ 10 ppm HCl	lifetime (27 mos.)	(27%) nasal tumors	NYU study of Laskin et al
Mouse, ♂ + ♀, $B6C3F_1$	inhal.	0 ppm 2.1 ppm 5.6 ppm 14.1 ppm	24 mos.	- (0%) - (0%) - (0%) (2%)	CIIT study of Swenberg et al, nasal tumors only
Hamster, ♂ Syrian	inhal.	10 ppm 30 ppm	lifetime	- (0%) - (0%)	Nettesheim, NCI - DOE study, 1977
Rat	s.c.[a]	formalin, 0.4%, 1 ml per animal weekly	15 mos.	(40%)	Watanabe et al, Gann, 45, 451 (1954) sarcomas at injection site only.
Rat	s.c.	HMT,[b] 40%. 2 ml per animal per week	until tumor development	(40%)	Watanabe et al, Gann, 46, 365 1955 sarcomas at injection site.
Rat, ♂+ ♀ BD	oral gavage	HMT, 0.4 g/day	12 mos.	(0%)	Brendel, Drug Res., 14, 51 (1964)
Mice (CTM, SWR, and C3Hf) and Rat (Wistar)	drinking water	HMT, 2.5 g/Kg/d	1 yr 2 yr	(0%) (0%)	Della Porte et al, Food Cosmetic Tox., 6, 707 (1968)[c]

Table I (continued)

Notes to Table:

a - sc = subcutaneous injection

b - HMT = hexamethylene tetramine

which decomposes in aqeous solution to give formaldehyde and ammonia with the stoichiometry:

$$1\ \text{HMT} \rightleftharpoons 4\ NH_3 + 6\ CH_2O$$

One gram of HMT is equivalent to 1.3 gram of free formaldehyde.

c - Della Porte et al, Tumori, 56, 325 (1970) also report a 3 generation study on Wistar rats with 2% HMT in drinking water which was negative for all three generations. This level of HMT is equivalent to about 2.5 g/Kg/d of ingested HMT which would be 3.3 g/Kg/d of formaldehyde.

The two studies used different strains of rat but are in general agreement. The CIIT study also exposed mice to formaldehyde gas but no statistically significant increase in tumors was observed. (See footnote 2.)

Other studies (some in other species and/or by other routes) have been generally negative save for a rat study of 1954 (expanded in 1955) using a subcutaneous injection route for 0.4% formalin or up to 40% hexamethylene tetramine (HMT, which gives rise to free formaldehyde, 1 gram HMT = 1.3 gram formaldehyde). In this study only sarcomas at the site of injection were found and these studies are not, therefore, generally accepted as being other than suggestive evidence of carcinogenecity. Significantly, the oral administration of hexamethylene tetramine to rats at up to 12.5 g/Kg/week was found to produce no tumors in three different investigations of up to two years duration (the same length as the CIIT inhalation study) conducted in 1964, 1968, and 1970. The oral route studies are somewhat limited by small sample sizes but, taking all three studies in aggregate, there is evidence which suggests a lack of a carcinogenic effect by this route. An important observation is that inhalation by hamsters at similar or higher exposure levels than used in the CIIT study has given a negative result. Formaldehyde appears, therefore, to exhibit considerable species specificity with the rat, the most sensitive of species so far tested.

Concern that formaldehyde gas may induce tumors in humans should be tempered by this observation that formaldehyde carcinogenicity appears to have a high degree of species specificity and a strong dependence on route of exposure. The rat, an obligatory nose breather, appears to have a particular nasal sensitivity to the deleterious effects of formaldehyde which may not be generally shared by other animals (man is not an obligate nose breather) or body sites. Based on the animal experimentation data, the most reasonable interpretation is that formaldehyde has carcinogenic potential, is probably locally acting, and is capable of both initiation and promotion.

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(2) The statistical significance of the CIIT results at 5.6 ppm in the rat (1.9% incidence observed) and 14 ppm in the mouse (2% incidence observed) was determined by CIIT as described in the CIIT document "Data Released to the International Agency for Research on Cancer (IARC) Working Group", dated October 19, 1981, which is appended as Appendix A.

The results of the CIIT bioassay are, however, sufficient to establish that formaldehyde is a potential animal carcinogen with mode and degree of exposure quite important to the toxic outcome. Based on the observed differences in response shown by rats, mice, and hamsters, different species have differing sensitivities. This may be a quantitative rather than a qualitative difference but the negative results of inhalation studies with Syrian hamsters at up to 30 ppm formaldehyde suggest that there may be qualitative differences in response among species as well. It can, however, be prudently expected that under appropriate conditions of exposure formaldehyde gas may pose a cancer risk to the respiratory tract of humans (i.e.: nasal and buccal cavities, trachea, bronchial trees, and lungs, see footnote 3). In the CIIT bioassay (see Appendix A), the development of nasal carcinomas was always preceded by hyperplasia, metaplasia and overt signs of cytotoxicity to the nasal mucosa (simply put, the animals developed open sores in their nasal tissues after which tumors appeared). In other cases, with other chemicals, where tumors appear to be secondary to cytotoxicity, no observable effect levels of exposure have been postulated (see, for example, Weisburger, J. H. and Williams, G. M. in Casarett and Doull's Toxicology, 2nd ed., MacMillan, NY (1981)). Since formaldehyde has genotoxic properties, any simple analysis is complicated but the findings of the CIIT research team which supported the bioassay have bearing on the interpretation of the results of the bioassay:

(1) At low exposure levels or short exposure times the hyperplastic and metaplastic effects of formaldehyde exposure were reversible. This suggests that a higher exposure level or longer exposure time may produce a qualitatively different outcome with respect to carcinogenesis than would result from low level or short term exposure.

(2) Normal endogenous tissue levels of formaldehyde produced by metabolism range from 3-12 Ng/g tissue (3-12 ppm). Much of this appears to be bound up as adducts to glutathione, tetrahydrofolate, and proteins. From 10%-40% of the total tissue formaldehyde appears to exist as free formaldehyde (0.3 Ng/g - 4.8 Ng/g). A sustained exposure of 3 ppm formaldehyde in air is needed to double the endogenous level of formaldehyde.

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(3) Other body sites are theoretically possible targets but, due to a variety of studies demonstrating rapid metabolic conversion of formaldehyde at or near the sites of uptake (Maloney, 6, et al; Arch. Exp. Pharmacol., 250; 419-436 (1965); McMartin, K.E., Biochem. Pharmacol., 28; 645-649 (1979)) it is expected that the respiratory tract will be the principal, possibly sole, target organ at risk. A high degree of site concordance between humans and animals has been suggested by Tomatis (L. Tomatis et al, Cancer Research, 38; 877 (1978)).

(3) There appears to be an absence of cytotoxic effects of formaldehyde at or below 1.0 ppm in air.

(4) Radio-isotope tracer measurements indicate that absorption of formaldehyde gas from imspired air is essentially complete within the nasal cavities and formaldehyde gas does not reach the trachea, bronchi or lungs of rats at the exposures used in the CIIT study.

(5) Formaldehyde is a mutagen. As such it is a potential genetoxic carcinogen. Aldehydes, as a chemical class, are also promoters of carcinogenesis (Slaga, T. J., Sivak, A.; and Boutwell, R. K.; Mechanisms of Tumor Promotion and Cocarcinogenesis, Raven Press, NY, 1978). Formaldehyde can, then, potentially both initiate and promote the carcinogenic process. A promoting and/or cocarcinogenic effect of formaldehyde is supported by other studies cited in Table I, in particular the various New York University studies. Promotion generally requires repeated, long term exposure to the promoter and is reversible [(Weisburger, J. H. and Williams, G. M.; "Chemical Carcinogenesis" in Holland, J. F. and Frei, E. (eds): Cancer Medicine, 2nd ed., Lea and Febiger, Philadelphia, 1980)], may involve damage to cellular components (Slaga et al (supra), 1978), and is a requisite, at some point, to the carcinogenic process. When taken together with the observations reported by CIIT on the reversibility of hyperplastic and metaplastic effects (vide (1) supra) and an apparent cytotoxicity threshold (vide (3) supra) the degree to which formaldehyde promotes its own carcinogenesis may lead to qualitative, as well as quantitative, differences in response within different regions of the dose-response curve.

An argument can be made that any initiating effects of formaldehyde would, nonetheless, produce a population of latent malignant cells. These cells could then produce malignancies in response to other promoters (endogenous or exogenous) as the animals grew older. In such a case the difference in response to formaldehyde exposure at different exposure levels would be only quantitative and not qualitative. This argument is a classical one (See Weisburger and Williams, 1981, supra) and has some merit as a general argument. It needs to be discussed, however, in the context of formaldehyde as it affects the nasal mucosa.

Clearly, in the absence of detoxifying mechanisms, the endogenous levels of formaldehyde should be potentially capable of initiating some cells. The observed absence of nasal carcinomas in rodents as spontaneous tumors (for example, Dr. A. Upton communicates by letter of August 17, 1981, that in 14 years with 1,920 rats he has not observed a single grossly visible nasal carcinoma) indicates one of

four things: (a) no cells are in fact initiated by endogenous levels of formaldehyde or repair processes at low exposure are faster than processes leading to cell transformation; (b) there are not endogenous promoters available to allow expression of the transformed cells; (c) any cells initiated are lost before their malignant potential can be expressed or (d) the tumor incidence is so low as to be undetectable.

The first situation would de facto, define a practical threshold for genotoxicity. Formaldehyde is an endogenous metabolite and it is possible that mammalian cells may deal effectively with low levels of it.

The second situation could suggest that promotion by exogenous factors (formaldehyde could be one) was the controlling element in formaldehyde carcinogenesis. This would imply a lack of carcinogenic effects at exposures to exogenous factors which did not result in promotion. The observation, by CIIT, that tumor formation could be secondary to a formaldehyde induced cytotoxicity, hyperplasia, and metaplasia does suggest that the promoting effects of formaldehyde may be quite important. At low exposure levels the hyperplastic, metaphastic, and cytotoxic effects observed were reversible in the CIIT study.

The third situation is probably relevant to the question of formaldehyde carcinogenesis. Normally, the epithelia of the nasal mucosa loses matured cells which are then daily replaced by underlying stem cell layers. Thus, cells which might be initiated by formaldehyde could be lost from the epithelia before their malignant potential could be expressed. This possibility has not however, been addressed experimentally.

The fourth consideration may have some bearing but in a variety of studies (CIIT and those of Dr. Upton's colleagues at NYU) over 2,000 rats have been observed as a historical control. If nasal carcinoma occurs spontaneously in rats, its incidence would be very low. (See footnote 4)

The observed lack or low incidence of spontaneous nasal carcinoma in rats--given the endogenous levels of formaldehyde present--is probably explained by a combination of the above

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(4) One rat developing a tumor per 2,000 animals would be an incidence of 5×10^{-4}. This is not the same as the level of risk to rat or, possibly, human but suggests that individual risk from endogenous tissue levels of formaldehyde might be bounded by numbers of similar magnitude.

considerations. The net result is that there would appear to exist some lower bound to the observable carcinogenic effect of formaldehyde resulting from exposure to exogenous sources.

As such, the above considerations regarding endogenous levels of formaldehyde coupled with observations of CIIT of the reversibility of formaldehyde related effects at low exposure levels suggest that low level exposures (<1-2 ppm) probably would not present a significant risk of a carcinogenic outcome. The CIIT radio-isotope work also would suggest that carcinogenic risk from airborn formaldehyde could be restricted to the nasal and oral cavities. According to IARC documents there is nearly an 80% site concordance between humans and animals for those human carcinogens adequately testing in animal systems (L. Tomatis et al, Cancer Res. 38, 877 (1978)).

Considertion of Existing Epidemiology Data - A number of small scale retrospective epidemiology studies on groups occupationally exposed to formaldehyde have found no excess of cancers of any type, in particular nasal or oral, in these groups which can be attributed to formaldehyde exposure when corrected for smoking and drinking. The annual incidence of human nasal cancer is about one in one million (1×10^{-6}). While I recognize the limits of sensitivity inherent in epidemiology, such data are useful. In particular, for chemicals of long standing and well defined use, epidemiology could tell if a critical situation exists. If formaldehyde were a potent human risk, this should show up epidemiologically. There does not appear to be any relationship, based on the existing data base on humans, between exposure and cancer. Real human risk could be considered to be low on such a basis.

Human Exposure to Formaldehyde - Human exposure to formaldehyde is at levels generally much lower than those used in the rat inhalation studies. Typical values are ca. 0.005 - 0.3 ppm in ambient air in urban areas, 0.0004 - 0.005 ppm in rural locations, and 0.1 ppm in urea-formaldehyde (UF) foam insulated dwellings. It has not been possible to demonstrate a statistically significant difference in exposure levels in UF foam homes as opposed to non-UF homes. Occupational exposures can be higher but are generally less than 2 ppm formaldehyde. These occupational exposures are, also, for short periods and of an intermittent nature. Table II presents a distribution analysis of exposure levels.

TABLE IF FREQUENCY DISTRIBUTION OF EXPOSURE ESTIMATES IN FORMALDEHYDE PRL-1 TECHNICAL DOCUMENT

These data are extracted from the integrated exposure assessment in the PRL-1. Only estimates given for populations of a known size are considered. High and low refer to the upper and lower bounds of estimated exposure ranges.

INTERVAL (ppm)	Number of estimated exposed individuals			
	Low	Percentage of Total Individuals Exposed	High	Percentage of Total Individuals Exposed
0 - 0.1[b]	2.24×10^8	99.4[a]	2.20×10^8	97.6[a]
0 1 - 0.5	7.09×10^4	0.03	4.50×10^4	0.02
0.5 - 1.0	3.00×10^4	0.01	-	-
1.0 - 2.0	3.04×10^4	0.01	5.89×10^4	0.03
2.0 - 5.0	1.24×10^6[c]	0.55	3.86×10^6[d]	1.71
5.0 -	-	-	1.26×10^6[e]	0.56

a/ % of total individuals exposed

b/ includes U.S. population via ambient air

c/ 97% are college students who on an average are exposed to an estimated 8.3 ppm for very short periods and over a limited time. Humans cannot tolerate formaldehyde exposures above 5 ppm and so this group is probably exposed to far less than the PRL-1 average estimate.

d/ 57% are mobile home residents at an average 0.4 ppm; 40% are U.F. home residents at an average of 0.72 ppm

e/ 95% are the same college students as in footnote c.

Humans do not adapt to levels of airborne formaldehyde over 5 ppm and levels from 2 - 5 ppm are generally very unpleasant. The "high" side of the PRL-1 exposure ranges should, then, be viewed critically as this suggests a very sizeable group is exposed - on a regular basis - to levels of formaldehyde above 2 ppm. It must be noted that for the group footnoted as (d) in Table II, the "high" value derives from short transients in complaint homes and is non-representative. The appropriate averages are indicated in the footnote. The exposure group footnoted as (e) in Table II, similarly is constituted by using a single excursion, transient as an upper bound on the range of exposure. The footnote (c) explains that PRL-1 assigned these college biology students an average exposure of 8.3 ppm several hours a week. Clearly, this number is not to be relied on since humans cannot breathe in such an environment. The column listed under "low" is to be taken as more representative (with the possible exception of the college biology students). Table II suggests, then, that nearly all prolonged human exposures are at levels well below 2 ppm.

Given that quantitative and possibly qualitative results of exposure to formaldehyde appear to depend highly on exposure level, species, and route; that rats seem to be particularly sensitive to formaldehyde; and that long human experience does not seem to indicate any pressing concerns; I must concur with OTS' staff recommendations in this matter - that formaldehyde ought not be considered subject to TSCA section 4(f) at this time.

Deficiencies in the Original OTS PRL-1 Document:

The original review of formaldehyde (PRL-1) was deficient in a number of areas -

(1) Exposure Estimates: This was the major deficiency in the original document. In many situations the exposures given were not obtained by analytical methods similar to that used to monitor formaldehyde levels in the CIIT study. No attempt was made to address the comparability of methods so it is not clear that 1 ppm by any given method equates to 1 ppm exposure under the CIIT protocol. This has the effect of making any subsequent risk analysis (which must be exposure based) an "apples and oranges" comparison. Table III points out the various methodologies cited in studies covered by the PRL-1 document.

TABLE III: Number of Exposure Estimates by Type of Analytical or Collection Method in Formaldehyde PRL-1

METHOD	NUMBER OF ESTIMATES	BASED ON METHOD[a]
		as % of all studies
Acetylacetone	1	1.1%
Bisulfite impingers	18	20.7%
Chromotropic acid	17	19.5%
Chemiluminescence	3	3.4%
Colorimetry	7	8.0%
Charcoal tubes	9	10.3%
Solid sorbents	1	1.1%
Draeger Tubes	3	3.4%
FT Spectroscopy	2	2.3%
Gas Chromatography	1	1.1%
Ion Chromatography	7	8.0%
MBTH Method	1	1.1%
Spectrophotometry	3	3.4%
Not Known	14	16.1%

[a]Number of studies in data base which cite a particular method. Some studies cite more that one method.

The PRL-1 review also used the highest values of formaldehyde found in any given monitoring study as its exposure levels for risk analysis. This is not well advised since these high levels are in most cases transients or single excursion values (i.e.: not continuous) and do not, therefore, represent the risk picture adequately. The tendency of the PRL-1 to use exposure levels greater than 2 ppm when calculating exposure to some populations is flawed as well since humans do not well tolerate exposures to formaldehyde which are higher than around 2 ppm. Even though some adaptation can occur, this is unknown above 5 ppm yet PRL-1 uses exposure levels above 5 ppm as prolonged exposures.

The poor quality of the exposure estimates is repeatedly acknowledged in the PRL-1 and forms the basis for the recommendations contained in the earlier draft Federal Register notice and action memorandum (see below). As such, any risk estimates given in the PRL-1 must be viewed very skeptically. It is not clear that such estimates would be a reasonable basis to do other than conclude that one needed better exposure data. This, in effect, is what OTS staff originally concluded and is in the earlier Federal Register notice draft of which NRDC has a copy.

(2) Evidence for Carcinogenecity: The PRL-1 concludes that formaldehyde is an animal carcinogen. It downplays a number of negative bioassays which suggest that its effects may depend highly on species, route and site. No attempt was made, also, to address the question of mechanism of action or other physiological/biochemical questions relevant to the extrapolation from rat to human even though such information was available from CIIT.

The discussion of human epidemiology emphasized studies which showed marginal differences in total cancer rates (i.e., the treatment of one study in which one cohort had a slight increase in total cancer tate relative to historical controls but a second cohort showed no such effect. Much was made of the "positive" cohort but the negative cohort was downplayed). No trend was seen toward increases in any specific cancer (as is common for human chemical carcinogens) in any study. The human data do not show signs (such as correlation to a specific tumor) usually seen for a human carcinogen and do not, as is discussed above, generally suggest any specific effect of formaldehyde.

Risk Assessment:

The PRL-1 document contained a risk assessment performed by use of the Crump multistage model and based on the high exposure estimates presented in the PRL-1 document. OTS staff has also calculated a risk analysis based on median (more representative) exposure values. Relative risks are calculated and expressed as 95% upper confidence limits on lifetime risks.

Table IV presents a population distribution of relative individual risks as calculated by OTS staff in PRL-1 using representative (median or average) exposure estimates. Risk is divided into order of magnitude ranges and the size of the affected population falling into each range is given. As can be seen nearly all individual risks fall into the range 1×10^{-6} - 1×10^{-4}. This places them into a range in which priority action is often not considered. A similar situation exists for populations of unspecified size (Table V). Again, if the human risk were real, the magnitudes of individual risks do not seem to compel a "fast track" approach. This seems to have been recognized in the draft FR notice prepared in 1981 by OTS under Dr. Muir. That notice proposed to engage in a two year effort to collect exposure data so as to refine the risk calculations. This stemmed from the poor quality of the exposure analysis in PRL-1 and the low relative magnitude of the estimated individual risks.

The risk calculation used by OTS included the 5.6 ppm exposure level as a non-zero incidence data point. CIIT has since determined this point to be statistically no different than the 0 ppm and 2.1 ppm exposure results (see Appendix A). If this 5.6 ppm exposure were treated as a zero response point, the risk estimates of Tables IV and V would shift, in distribution, to yet lower values.

The risk estimates in PRL-1, also, do not take into account that tumor formation in rats appears to require a long term, high level exposure and that the human exposures are likely to be relatively short. Workers might see 1 ppm or less intermittently over a 40 year work career assuming no change in occupation (see footnote 5). College students in biology

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(5) The OSHA standard for formaldehyde is 3 ppm but OSHA documents indicate that workplace exposures are generally less than 1.5 ppm. OPTS staff agree that this is an appropriate and representative number as a general upper bound on workplace exposures.

TABLE IV: DISTRIBUTION OF RELATIVE INDIVIDUAL LIFETIME RISKS AS DERIVED FROM PRL-1 FOR FORMALDEHYDE

Range of Risk	Population Size[a]	% of Total	
		A	B
10^{-6} - 10^{-4} (0.003)[b]	2.14×10^{8}	99.9	95.0
10^{-4} - 10^{-3} (0.15)	1.52×10^{5}	0.071	4.1
10^{-3} - 10^{-2} (1.5)	3.13×10^{4}	0.015	0.9
10^{-2} (3)	0	-	-

A: Total of all identified populations

B: Excluding ambient air and water exposures

[a]This table applies only to exposed populations for which a size was estimated in PRL-1

[b]NCI data indicate that individuals of the U.S. population have an average individual lifetime risk of contracting cancer of 3.3×10^{-1}, the number in parenthesis is the % increment above this average represented by a risk in the center of each indicated range save for the last range in which case the % increment is that due to the boundary risk.

TABLE V: DISTRIBUTION OF GROUPS WITH UNSPECIFIED POPULATION SIZE BY RELATIVE RISK INTERVALS

Both maximum likelihood and 95% upper confidence estimates of relative individual lifetime risk are shown. For comparison, according to recent National Cancer Institute figures the absolute risk of contracting cancer over a lifetime is approximately 1/3 or 3.3×10^{-1}. For each risk interval the percentage increase in lifetime risk (assuming the risk estimates are absolutes which they are not) is presented.

Interval		Number of size	Undetermined groups
range	% incremental[a]	MLE[b] Maximum likelihood estimate	ULOC[c] Upper Limit of Confidence
$<10^{-5}$	0.003%	6	0
$10^{-5} - 10^{-4}$	0.03%	3	7
$10^{-4} - 10^{-3}$	0.3%	2	3
$10^{-3} - 10^{-2}$	3%	0	1[d]

a/ % increment above NCI determined lifetime risk of 3.3×10^{-1}

b/ Maximum likelihood estimate

c/ Upper limit of 95% confidence

d/ Represents one group with a 20 fold range in estimated exposures.

labs are, similarly, a large group (1.2 million individuals) which the PRL-1 assumes are exposed over 70 years. In fact, exposure of nearly all of these students would be generally on the order of one year or less.

Another factor not considered in the PRL-1 risk estimates is that the animal evidence would suggest that inhalation of formaldehyde by humans should produce tumors (if any are seen) primarily of the oral, pharyngeal and nasal mucosa (see footnote 3). These are well defined sites for which the limited epidemiological evidence does not suggest an association with formaldehyde exposure under what are poorly documented but probably representative conditions.

In summary, the PRL-1 does serve to identify some possible areas of concern. From a technical standpoint it would appear to be premature to "fast-track" any regulatory actions since we have estimates only on the upper bound of any risks and these do not, when reasonable assumptions are made, appear to be significant. The draft FR notice (discussed below) which was prepared by OTS on the basis of PRL-1 review acknowledged as much by specifying no regulatory actions per se. The proposed response was, rather, to conduct monitoring surveys of the actual exposure conditions so as to better quantitate the risk. This de facto recognizes that the PRL-1 numbers were highly unreliable and that a proper risk assessment had yet to be done. PRL-1 does not seem to sustain a reasonable conclusion that formaldehyde presents a significant risk of cancer to humans.

Deficiencies in the draft Federal Register notice on formaldehyde:

In 1981 OTS drafted a proposed Federal Register notice on formaldehyde for the signature of the Administrator.

This notice presented a logical sequence and I have analyzed the rationale employed as follows:

(A) Formaldehyde is an animal carcinogen;

therefore,

(B) it is a potential human carcinogen.

(C) Formaldehyde is a high volume chemical;

therefore,

(D) it presents wide spread exposure potential.

(E) Some individual exposures are estimated to be high;

therefore,

(F) some exposures are serious.

Given (B), (D) and (F), then

(G) Formaldehyde is a potential human carcinogen that presents serious or widespread exposures;

therefore,

(H) formaldehyde meets the section 4(f) criteria for "significant" risk of "serious" or "widespread" harm.

There are a number of flaws in this line of reasoning. Some are explicitly acknowledged in the draft FR notice but others are more subtle and need to be addressed first:

(1) The meaning of the term "significant" in the draft FR notice is not consistent with the common technical meaning as discussed above. No case is made for other than formaldehyde being a potential or possible human carcinogen. The degree to which this may or may not be an actuality (i.e., the significance of this risk in terms of probability of existence and magnitude if it exists--as discussed under Technical Issues above) is not addressed. Therefore the draft FR notice uses the words "significant" and "potential" synonymously.

(2) The assumption that a high production volume equates with a high or "widespread" exposure potential is very weak. In general, the degree of correlation between production volume and exposure will depend on uses and handling methods. A blanket assumption, as used in the FR draft notice, is not justifiable in the absence of supporting evidence.

(3) The conclusion that some individual exposures are "serious" is premised on faulty assumptions as to exposure levels as previously discussed.

The plain language of the statute calls for initiation of regulatory action under sections 5, 6 or 7 as the response to be made under section 4(f). The proposed gathering of exposure data--the response given by the FR draft--appears to be an acknowledgement that the significance of any risk from formaldehyde has not been reasonably evaluated since, as a result of gathering this exposure data, it is further proposed to evaluate risk to see if further action is appropriate. The premises and conclusions in the FR draft appear to be faulty.

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DEHP:

No detailed analysis is presented of the DEHP situation since work culminating in the PRL-1 and draft Federal Register documents was based on incorrect exposure assumptions. The policy analysis given in the section on formaldehyde applies to the DEHP case.

For purposes of discussion and comparison, the risk estimates in the PRL-1 document are given and then discussed briefly:

Table: PRL-1 Risk Estimates

Group	70 yr Individaul Risks	Potential Cases[a] Over 70 years
hemodialysis patients (45,000)	1×10^{-3}	45
hemophiliacs (19,000)	1×10^{-4}	1.9
U.S. population via food (250 million)	7.5×10^{-7}	188
U.S. population via drinking water (250 million)	6×10^{-7}	150
[b]Occupational (as in PRL-1 originally)		
Manufacturing (335)	1×10^{-4}	0.03
Processing (40,000)	1×10^{-4}	4
[b]Occupational (as revised by OTS)		
Manufacturing (335)	1×10^{-5}	0.004
Processing (40,000)	1×10^{-6}	0.04

a Assumes 95% upper confidence limit is an absolute risk, it is in fact relative and an upper bound on any relative risk present.

b Revised on the basis of exposure data presented at the 1980 pthalates conference.

It must be pointed out that the first two groups in the Table are not affected by TSCA since their exposure is a result of contact with medical devices under the purview of FDA. These are also groups

which are at high risk from their diseases and the benefits of these medical devices should probably far outweigh the risks indicated. In any case, they cannot be factored into any analysis of TSCA applicability.

Estimates for the dietary risks to the U.S. population as a whole fall below the range in which regulatory agencies do not take any actions. The exposures were estimated as described in PRL-1 and are of good quality, in my opinion.

The drinking water estimate is the average number contained in PRL-1. I believe it to be representative and, again, the risks are below the range in which we would normally not act.

The original Federal Register document was driven largely by the occupational risks given in the table. The risks begin to push up into the range in which we would normally consider some action (regulatory or non-regulatory) but are, nonetheless, lower than what might push a priority designation. As a result of the 1980 phthalates conference, OTS staff realized that the exposure estimates which had been used to generate these risks were completely incorrect. In essence they postulated a DEHP concentration (as vapor in air) higher than the vapor pressure of DEHP could generate.

The exposures and associated relative risks were recalculated and are given in the PRL-1 Risk Estimates Table as revised occupational risks. With the revision of the occupational exposure numbers reason to take any action with respect to DEHP disappeared.

There has not, since the detection of the errors in occupational exposures, been any reasonable basis upon which DEHP could be considered to pose significant risk to humans - given current use patterns - and I concur with OTS staff that DEHP cannot be recommended to you as a candidate for section 4(f) designation.

As a final comment on DEHP, there are enough anomalies in the result of the NCI bioassay that I remain unpersuaded that DEHP should be considered a human carcinogen.

Appendix A

DATA RELEASED TO

THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC)

WORKING GROUP

OCTOBER 19, 1981

Chemical Industry Institute of Toxicology (CIIT)
P. O. Box 12137
Research Triangle Park, NC 27709

FORMALDEHYDE

3.1 Carcinogenicity studies in animals

(b) Inhalation and/or intratracheal administration

Mouse

Groups of 120 male and 120 female B6C3F1 mice, 6 weeks of age, were exposed to 0, 2.0, 5.6 or 14.3 ppm (0, 2.46, 6.89, 17.59 ng/m^3) formaldehyde (> 97.5% pure) vapor by whole-body exposure for six hours per day on 5 days per week, for up to 24 months. A 90 day sub-chronic study utilized to set the exposure levels demonstrated necrosis of the nasal mucosa and death after 2 weeks exposure to 40 ppm. The number of mice involved in scheduled sacrifices and unscheduled deaths is shown in Table 1. All tissues from control and high exposure mice and multiple sections of nasal cavity and all gross lesions from all low and mid-exposure mice, as well as all tissues from unscheduled deaths in these groups were evaluated histopathologically.

Concentration related effects of formaldehyde exposure on mouse survival were not apparent, however, substantial mortality did occur in all groups of male mice. This was primarily attributed to fighting and ascending urinary tract infections. Exposure of mice to 14.3 ppm formaldehyde vapor resulted in diminished body weight. Using life-table analysis, a number of lesions in the nasal cavity were significantly increased ($p < 0.0167$). These lesions included epithelial dysplasia at 5.6 and 14.3 ppm in males and females; squamous metaplasia at 5.6 and 14.3 ppm in males and 14.3 ppm in females; purulent or seropurulent rhinitis at 14.3 ppm in males and females; and olfactory epithelial atrophy in 14.3 ppm female mice. Squamous cell carcinomas occurred in the nasal cavities of 2 male mice, but no females. Neither life-table analysis nor the Fischer exact test revealed statistical significance (Kerns et al., 1982a,b).

Table 1. Number of formaldehyde-exposed mice involved in scheduled sacrifices and unscheduled deaths

Exposure (ppm)	Sex	Scheduled Sacrifice					Unscheduled Deaths		Total
		6 mo	12 mo	18 mo	24 mo	27 mo	0-24 mo	24-27 mo	
0	Male	10	10	0	21	0	78	0	120
0	Female	10	10	20	31	16	30	4	121
2.0	Male	10	10	1	22	0	77	0	120
2.0	Female	10	10	20	26	12	34	8	120
5.6	Male	10	10	0	19	0	81	0	120
5.6	Female	10	10	20	41	11	19	9	120
14.3	Male	10	10	0	17	0	82	0	119
14.3	Female	10	10	19	28	9	34	11	121

Rats

Groups of 120 male and 120 female Fischer 344 rats, 7 weeks of age were exposed to 0, 2.0, 5.6 or 14.3 ppm (0, 2.46, 6.89 or 17.59 ng/m^3) formaldehyde (> 97.5% purity) vapor by whole-body exposure for six hours per day on 5 days per week, for up to 24 months. A 90 day sub-chronic study utilized to set the exposure levels demonstrated weight loss and mucosal erosions of the nasal turbinates in rats exposed to 12.7 ppm and mortality and ulceration of the nasal turbinates and trachea after 2 weeks of exposure to 40 ppm. The number of rats involved in scheduled sacrifices and unscheduled deaths is shown in Table 2. All tissues from control and high exposure rats and multiple sections of nasal cavity and all gross lesions from all low and mid-exposure rats, as well as all tissues from unscheduled deaths in these groups, were evaluated histopathologically.

Rat survival was adversely affected by exposure to 14.3 ppm. A summary of neoplastic lesions in the nasal cavity is shown in Table 3. Life-table analysis of these data revealed significant increases ($p < 0.0167$) in squamous cell carcinomas in both male and female rats exposed to 14.3 ppm formaldehyde vapor. Significant increases in other neoplasms were not detected in formaldehyde exposed rats. A variety of other lesions were significantly increased in formaldehyde exposed rats. These included epithelial dysplasia at 2, 5.6 and 14.3 ppm in males and females; squamous metaplasia at 2, 5.6, and 14.3 ppm in males and females; goblet cell hyperplasia at 2, 5.6, and 14.3 ppm in males and at 2 ppm and 14.3 ppm in females; hyperkeratosis at 14.3 ppm in males and females; purulent or seropurulent rhinitis at 2, 5.6, and 14.3 ppm in males and at 5.6 ppm and 14.3 ppm in females; squamous atypia at 14.3 ppm in males and females; olfactory epithelial atrophy at 14.3 ppm in males and females; respiratory epithelial hyperplasia at 14.3 ppm in males; goblet cell metaplasia of the olfactory epithelium at 14.3 ppm in males and females; and squamous epithelial

hyperplasia at 14.3 ppm in males. The incidence of tracheal epithelial dysplasia and metaplasia was different from control animals at 14.3 ppm in both males and females. The incidence of squamous metaplasia in the nasal cavity in rats from the 2.0 and 5.6 ppm exposure groups regressed during the three month postexposure period (Swenberg et al., 1980; Kerns et al., 1982a,b).

Table 2. Number of formaldehyde-exposed rats involved in scheduled sacrifices and unscheduled deaths

Exposure (ppm)	Sex	Scheduled Sacrifice						Unscheduled Deaths		Total
		6 mo	12 mo	18 mo	24 mo	27 mo	30 mo	0-24 mo	24-30 mo	
0	Male	10	10	20	54	10	6	6	4	120
0	Female	10	10	20	47	9	4	13	7	120
2.0	Male	10	10	20	50	10	4	10	6	120
2.0	Female	10	10	20	44	10	1	16	9	120
5.6	Male	10	10	20	41	10	3	19	7	120
5.6	Female	10	10	20	41	9	5	19	6	120
14.3	Male	10	10	20	13	5	0	57	4	119
14.3	Female	10	10	19	14	0	0	57	0	120

Table 3. Summary of neoplastic lesions in the nasal cavity of Fischer-344 rats exposed to formaldehyde vapor.

Exposure group (ppm)	0		2.0		5.6		14.3	
Sex	M	F	M	F	M	F	M	F
No. of nasal cavities examined	118	114	118	118	119	116	117	115
Squamous cell carcinoma	0	0	0	0	1	1	51[a]	52[a]
Nasal carcinoma	0	0	0	0	0	0	1[b]	1
Undifferentiated carcinoma or sarcoma	0	0	0	0	0	0	2[b]	0
Carcinosarcoma	0	0	0	0	0	0	1	0
Osteochondroma	1	0	0	0	0	0	0	0
Polyploid adenoma	1	0	4	4	6	0	4	1

[a]Significantly increased over 0, 2.0, and 5.6 ppm (adjusted Cox-Tarone $p < 0.0167$).

[b]One animal also had a squamous cell carcinoma

3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

Acute cell degeneration, necrosis and inflammation, were evident in the nasal cavities of rats exposed to 15 ppm formaldehyde vapor for 1 to 9 days (6 hrs/day) (Swenberg et al., 1982). Initial lesions were most severe on the tips of the maxillo and nasoturbinates. Acute degeneration and sloughing of the respiratory epithelium, with edema and congestion were evident at the end of 1 day's exposure. This was followed by ulceration, necrosis and an influx of inflammatory exudate at days 3-9. Early squamous metaplasia was detetted over the naso- and maxilloturbinates, median septum and lateral wall after as little as 5 days of formaldehyde exposure. Examination of turbinates from rats exposed 5 days and allowed to recover for 48 hours demonstrated considerable regeneration. Areas which were frequently ulcerated, such as the lateral wall, had single thin strap cells covering areas normally occupied by 5 or more cuboidal epithelial cells. In contrast to these changes in the respiratory epithelium, mild serous rhinitis was the principal lesion in regions of olfactory epithelium. Mild degenerative and inflammatory changes were also evident in the nasopharynx.

The mouse was similar, but less severe than the rat in its acute response to formaldehyde toxicity. Five days exposure to 15 ppm formaldehyde vapor caused degeneration, focal necrosis and inflammation to the naso- and maxilloturbinates and to the lateral wall, but minimum toxicity to areas lined by squamous and olfactory epithelium. By comparing these acute data with results from the 6 month interim sacrifice (Kerns et al., 1982a,b), it is clearly evident that adaptive changes have occurred. The extent and severity of formaldehyde-induced toxicity diminishes with time. This may be due to changes in respiratory

physiology, as well as alterations at the cellular level, ie. squamous metaplasia, epithelial hyperplasia and increased detoxification pathways.

Effects of formaldehyde exposure on cell turnover

A prominent response to cell loss associated with toxicity is compensatory cell replication. Surviving cells undergo division in order to replace dead cells. Exposure of rats to formaldehyde vapor for 3 days (6 hrs/day) resulted in increased cell replication in rats at 6 and 15 ppm and mice at 15 ppm. No increase was detected in rats exposed to 0.5 or 2 ppm or mice exposed to 0.5, 2 or 6 ppm (Swenberg et al., 1982).

Studies on the distribution and metabolism of formaldehyde in the nasal cavity

Biochemical investigations on the absorption and distribution of ^{14}C-formaldehyde have demonstrated that H_2CO is primarily absorbed in the upper respiratory system (Heck et al., 1982). Following a 6-hr exposure, the amount of $^{14}CH_2O$ absorbed appears to be directly proportional to the airborne concentration. This result is consistent with the high water solubility of CH_2O. It is important as well that the amount of $^{14}CH_2O$ absorbed did not appear to vary following pre-exposure. Hence, these findings, which are based on single exposures, may also be relevant to the chronic toxicity of CH_2O.

The extensive distribution of radioactivity to other tissues indicates that absorbed $^{14}CH_2O$ or its metabolites are rapidly removed by the mucosal blood supply. It is, however, unlikely that this radioactivity is primarily due to $^{14}CH_2O$. Rapid metabolism in the blood and tissues would probably reduce the concentration of free CH_2O to extremely low levels.

The disposition and pharmacokinetic studies indicate that inhaled CH_2O is extensively metabolized. It is likely that folic acid plays an important, perhaps a pre-eminent, role in this incorporation. However, the possibility that $^{14}CH_2O$ may form covalent adducts *in vivo*, or that $^{14}CO_2$ may itself be incorporated via carboxylation reactions cannot be excluded. The metabolism of inhaled $^{14}CH_2O$ appears to be similar to that which occurs following other routes of administration.

In order to localize this absorption within the nasal cavity, naive or pretreated rats and mice were exposed to 15 ppm ^{14}C-formaldehyde for 6 hours and prepared for whole-body autoradiography. Formaldehyde-associated ^{14}C was heavily deposited in the anterior nasal cavity of rats and mice. The amount of radioactivity correlated well with the distribution of lesions in similarly exposed animals. That is, activity was greatest in regions of respiratory epithelium over the maxillo- and nasoturbinates and the lateral wall. An exception was noted for the ventral portion of the nasal cavity lined with squamous epithelium. Radioactivity was heavily deposited in this area, however, minimal toxicity occurred. This is most likely accounted for by the relative insensitivity of squamous epithelium to formaldehyde intoxication and supports the concept that induction of squamous metaplasia is a host defense mechanism to formaldehyde toxicity. A portion of the radioactivity located in the ventral squamous regions may be the result of muco-ciliary flow and gravity, rather than direct exposure to formaldehyde vapor. As such, the radioactivity may represent covalently bound material rather than reactive formaldehyde. The extent of formaldehyde-associated radioactivity deposited in regions of olfactory mucosa of posterior sections of the nasal cavity was much less, with radioactivity primarily confined to the nasopharynx. No differences were apparent in formaldehyde distribution between naive rats and mice. When animals that had been

exposed to 15 ppm of non-radioactive formaldehyde for 9 days prior to exposure to ^{14}C-formaldehyde were compared to the naive rats and mice, the pretreated mice had less radioactivity (Swenberg et al., 1982).

This decrease in radioactivity is associated with a decrease in minute volume in mice exposed to formaldehyde (Barrow et al., 1982). If the minute volumes for rats and mice exposed to 15 ppm formaldehyde are used to calculate the amount of formaldehyde inspired, and this amount is normalized to the surface area of the nasal cavity (Gross et al., 1982), the "dose" of formaldehyde available for absorption is 0.154 and 0.075 ug/min/cm^2 in rats and mice, respectively (Barrow et al., 1982; Swenberg et al., 1982). Thus, the mouse nasal mucosa is exposed to half the amount of formaldehyde than the rat nasal mucosa is. This dose correlates well with tumor data, where the incidence of nasal carcinoma is similar in rats exposed to 5.6 ppm and mice exposed to 14.3 ppm of formaldehyde vapor (Kerns et al., 1982b).

Mutagenicity and other short-term tests

The effects of formaldehyde were evaluated in the C3H/10T½ Cl 8 cell transformation system. Treatment of cells with 0.1 - 2.5 ug/ml of formaldehyde alone did not result in significant rates of transformation. If formaldehyde treatment was followed by continuous treatment with 0.1 ug/ml of the tumor promoter 12-O-tetradecanoyl phorbol-13-acetate (TPA), transformed foci were produced. Methanol and formic acid lacked significant transforming activity under either treatment regimen. The results suggest that formaldehyde is an initiating agent for C3H/10T½ Cl 8 transformation (Ragan and Boreiko, 1981; Boreiko and Ragan, 1982; Boreiko et al., 1981).

has been shown to cause DNA-protein crosslinks in mouse L1210
., 1981; Ross and Shipley, 1980) and V79 cells (Swenberg et al.,
rotein crosslinks were repaired within 24 hours in both cell

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APPENDIX C

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

March 4, 1982

OFFICE OF
THE ADMINISTRATOR

Dr. George A. Keyworth
Science Advisor to the President
Office of Science and
Technology Policy
Executive Office of the President
Washington, D.C. 20500

Dear Jay:

EPA has recently released the analysis it used in reaching a decision on formaldehyde's possible classification as a priority chemical. I have enclosed a copy of our findings. I would like to share our thinking and future plans with respect to formaldehyde with you and representatives of other concerned Federal agencies. I have also sent copies of our analysis to appropriate people in these agencies.

The Office of Toxic Substances (OTS) has found that formaldehyde should not be treated as a priority chemical for regulatory action under Section 4(f) of the Toxic Substances Control Act (TSCA) as it does not meet the statutory tests of that section. The OTS analysis does note that there could be other, non-section 4(f) health concerns (given formaldehyde's irritant properties). There also exists a possibility that there could be some, as yet unidentified, segment of the population whose exposure might raise a question of carcinogenic risk that the Agency may have interest in pursuing.

The Agency is continuing to gather and exchange information with other agencies and the public sector. We are fortunate in the case of formaldehyde that so much research has been initiated to better understand the mechanism of its toxicity, both in experimental animals and humans.

We plan to review information needed to evaluate human health risks from exposure as the ongoing research on formaldehyde is completed. During this period, our interface with other regulatory agencies will keep us abreast of possible new exposure situations which may be within the domain of EPA's legislation.

Currently, there is an ongoing effort in OTS to maintain a presence in the formaldehyde issue. This workplan includes an evaluation of the hazard, human exposure, and human risk associated with formaldehyde. The establishment of a mechanism for the exchange of formaldehyde information is also being developed.

I would like to ask that a meeting of the OSTP Regulatory Work Group on Science and Technology be held in the next two to three weeks to discuss multiple-agency information exchange on formaldehyde. A second topic would be funding of an outside peer review of ongoing formaldehyde studies. I have received an informal proposal on the peer review of formaldehyde (field and laboratory) studies from the National Academy of Sciences (NAS). This proposed NAS oversight-review would include studies being completed in an 18 month period from July 1, 1982 to December 31, 1983. Their study would require two years to complete during which approximately seven NAS reports would be written. This project would cost approximately $300,000 to complete and funding could come from either or both FY 83 and FY 84 funds.

I will be pleased to present the details of the NAS proposal and other possible approaches with the OSTP Inter-agency Staff Group at our next meeting. In this respect I ask that we schedule a session in the next two weeks.

Thank you for your help. With best wishes and warm regards.

Sincerely,

John W. Hernandez, Jr.
Deputy Administrator

Enclosure

APPENDIX D

Formaldehyde: A Question of Cancer Policy?

Frederica Perera and Catherine Petito

In what may constitute a test case for a new federal cancer policy, the Formaldehyde Institute, an association of formaldehyde producers and users, has advocated that formaldehyde not be regulated by the federal government despite recent studies showing that the substance causes tumors in animals and despite evidence that there is considerable human exposure to formaldehyde. The institute has argued that the animal data do not provide a sufficient basis to regard formaldehyde as a likely human carcinogen and that federal regulatory agencies should await the development of conclusive human (epidemiological) data before taking protective action.

This position contradicts principles for assessing carcinogenic risk that have been widely accepted by the scientific community for over a decade and embodied in policies of regulatory agencies following deliberations of broad-based scientific panels. These principles assert that confirmed positive animal data are presumptive evidence of carcinogenicity in humans; that with current information and methods it is not possible to establish threshold or no-effect levels that can be reliably applied to the human population; and that positive human epidemiological data are not necessary to conclude that a chemical substance poses a significant human risk (*1*). In fact, federal agencies have regulated such substances as pesticides, hair dyes, food additives, and industrial carcinogens (for example, β-propiolactone and ethyleneimine) in the workplace primarily on the basis of results in experimental animals (*2*). These principles are consistent with the accepted social policy that it is preferable to err on the side of caution in interpreting the available scientific data in order to avoid failure to regulate a serious health hazard.

Thus, acceptance by federal agencies of the industry position regarding the risk posed by exposure to formaldehyde could overturn established procedures for assessing and regulating carcinogenic

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substances in general. During the last 8 months, Environmental Protection Agency (EPA) and Occupational Safety and Health Administration (OSHA) officials have reversed prior staff recommendations to initiate regulatory action to limit human exposure to formaldehyde (*3–5*). In February 1982, EPA declined to regard formaldehyde as a priority candidate for regulation under the Toxic Substances Control Act (TSCA)

Summary. This article describes recent events concerning the assessment and regulation of formaldehyde, and evaluates the scientific data pertaining to the carcinogenicity of this substance in the context of established cancer policies and guidelines. The conclusion is that recent decisions by several federal agencies to defer action to limit human exposure to formaldehyde may be a "test case" for a new, less protective policy concerning the regulation of carcinogenic substances in general.

on the basis that the animal data may not be relevant to humans, that there is an absence of positive human data, and that it has not been established that, at human exposure levels, the risk of cancer is "probable and would be high" (*6*). According to sources quoted in *Inside EPA*, not only does the agency's decision not to move quickly on formaldehyde reflect a "clear divergence from current federal policy," but "EPA Deputy Administrator John Hernandez has made tentative plans to totally revamp the agency's cancer policy." (*4*).

Our purpose in this article is to review in detail the data on the carcinogenicity of formaldehyde in light of established guidelines for assessment of carcinogenic substances to see the extent to which the recent federal agency decisions represent a major policy change.

Background

Formaldehyde (HCHO) is a versatile chemical used in the manufacture of such products as particle board, plywood, paper, home insulation, material polymers and resins, leather and agricultural products, permanent-press fabrics, preservatives, embalming fluids, drugs, and cosmetics. About 7 billion pounds of formaldehyde are produced each year, making it the 26th largest volume chemical in the United States (*7*). An estimated 1.4 million people are exposed to formaldehyde in the workplace; 11 million people may breathe vapors in the home released by construction and insulation materials; and virtually the entire population comes into contact with the chemical because of its ubiquitous presence in polluted air and in consumer products (*8*). Concentrations of more than 8 parts per million (*9*), 0.02 to 4.2 ppm (*8*), and 0.1 to 3.4 ppm (*10*) have been measured in the workplace, in mobile homes, and in U.S. houses insulated with urea-formaldehyde foam, respectively, while levels frequently range above 0.1 ppm in urban air (24-hour average) (*8*). The present U.S. occupational standard for formaldehyde is 3 ppm (time-weighted 8-hour average) (*11*).

Thus, in the fall of 1980 there was widespread recognition of the significance of an interim report from the Chemical Industry Institute of Toxicology (CIIT) that formaldehyde was carcinogenic in rats (*12*). According to the final report (*13*), at the end of a 30-month period squamous cell nasal carcinomas were observed in 103 of 232 rats exposed by inhalation to 14.3 ppm of formaldehyde, in 2 of 235 rats exposed to 5.6 ppm of formaldehyde, and in 2 of 225 mice exposed to 14.3 ppm of formaldehyde. No such nasal cancers were found in 236 rats exposed to 2 ppm of formaldehyde or in the control animals. Polypoid adenomas were reported in all exposure groups and in one male control rat. By February 1981, various groups of experts had reviewed the CIIT interim (*7*) data, including a federal panel convened at the request of the Consumer Product Safety Commission (CPSC) under the aegis of the National Toxicology Program (NTP) (*14*) and the Environmental Cancer Information Unit of the Mount Sinai School of Medicine (*15*). The NTP report stated that "Formaldehyde should be presumed to pose a risk of cancer to humans" in agreement with the Mount Sinai conclusion that

> HCHO is a carcinogen in rats and, data suggest, in mice at exposure levels comparable to those found in some home and work environments. These findings indicate that effective controls should be initiated to reduce or eliminate human exposure to HCHO [*15*, p. 9].

Meanwhile, experiments at New York University (NYU) (*16, 17*) showed that exposure of groups of 100 male rats to formaldehyde and hydrogen chloride separately and combined, at average concentrations of 14 ppm and 10 ppm, respectively, resulted in an excess of histologically confirmed nasal squamous cell carcinomas in rats exposed to HCHO alone and none in the controls or in the rats exposed to HCl alone. Combined exposure to HCHO and HCl produced about the same number of histologically confirmed nasal squamous cell carcinomas as HCHO alone (*16*). As in the CIIT study, no grossly visible spontaneous nasal tumors of this type had been observed in control rats at that laboratory over a period of many years (*17, 18*).

In the spring of 1981, on the basis of the CIIT study and a review of available data on formaldehyde use and human exposure to the chemical (*19*), EPA staff drafted a *Federal Register* notice under §4(f) of TSCA designating formaldehyde as a priority chemical for regulatory assessment (*20*). The draft 4(f) notice stated:

> EPA has determined that there may be a reasonable basis to conclude that some exposures to formaldehyde present a significant risk of widespread harm to humans. Therefore the Agency is initiating action to investigate those exposures of greatest concern and determine whether they lead to unreasonable risks [*20*].

The notice was not signed by the Administrator of EPA. Rather, during the summer of 1981 EPA Deputy Administrator John Hernandez convened a series of unannounced meetings—termed "science courts"—primarily attended by EPA and Formaldehyde Institute representatives in order to review the scientific data on formaldehyde (*21*). A congressional subcommittee was critical of this significant departure from the accepted peer review process (*3, 22*).

On 4 September 1981, the Natural Resources Defense Council (NRDC) requested an explanation of EPA's failure to act on formaldehyde under §4(f) of TSCA and notified the agency of its intention to seek judicial review of that failure under §20 of the act. On 11 September 1981, a memorandum from Don Clay, Office Director of the EPA Office of Toxic Substances (OTS), to John Todhunter, then Assistant Administrator Designate for Pesticides and Toxic Substances, recommended against treating formaldehyde as a priority for assessment under §4(f) of TSCA pending additional epidemiological information (*23*).

In parallel developments at OSHA, in July 1981 an OSHA official recommended reversal of a prior decision to release a bulletin on formaldehyde jointly with the National Institute for Occupational Safety and Health (NIOSH) (*24*). The NIOSH *Current Intelligence Bulletin* had stated that formaldehyde should be

handled as a potential occupational carcinogen and that appropriate controls should be imposed to reduce worker exposure (*9*). OSHA also denied a 26 October 1981 petition by the United Auto Workers (*25*) for an emergency standard for formaldehyde. OSHA's action in putting aside new standards on formaldehyde and other substances triggered concern that new officials at OSHA were likely to revise the agency's cancer policy (*5*).

On 17 August 1981, Arthur Upton, Chairman of the NYU Medical Center Institute of Environmental Medicine, wrote to the heads of federal agencies that formaldehyde is "decisively carcinogenic in animals" and "if the carcinogenicity of formaldehyde is ignored, it would mean that no agent could be regarded as carcinogenic in the absence of positive evidence in humans" (*17*). This letter prompted a response from Joel Bender, Chairman of the Medical Committee of the Formaldehyde Institute, that "to regard formaldehyde as a likely carcinogen in man is not supportable" (*26*). By contrast, in October 1981 a working group of the International Agency for Research on Cancer (IARC) concluded, on the basis of the CIIT and NYU studies, that formaldehyde gas is carcinogenic to rats and should be considered "for practical purposes," in the absence of adequate data in humans, as if it represented a carcinogenic risk to man (*27*).

On 29 January 1982, a detailed letter to the assistant secretary for OSHA, the EPA administrator, and the chairman of the CPSC from Upton of NYU and I. B. Weinstein of Columbia University recommended prudent measures to restrict exposure to formaldehyde:

> It has come to our attention that EPA, OSHA, and possibly other federal regulatory agencies, may be planning not to take immediate protective action on formaldehyde, in spite of substantial evidence for its carcinogenicity from animal bioassays. We are concerned about the possibility of such a departure from established public health policy. It would conflict with the prevailing views of the scientific community and would set a precedent which could hamper future regulatory action on other carcinogens.
>
> There is general agreement among experts in chemical carcinogenesis that a substance which causes cancer in significant numbers of experimental animals in well-conducted assays poses a presumptive carcinogenic risk to some humans, even in the absence of confirmatory epidemiological data. While negative human data can define the upper limit of risk to man, there is no recognized method as yet for establishing the existence of a threshold for a carcinogen in the human population. These principles, which are accepted throughout the world, have served for many years as the basis for sound public health policy and regulatory action on carcinogens.
>
> To compare our views on this subject with those of our colleagues, we have consulted several of the world's leading authorities on chemical carcinogenesis for their opinions. The replies we have received from them thus far are unanimous in supporting the principle that definitive demonstration of carcinogenicity in well-conducted animal bioassays suffices to provide evidence of presumptive carcinogenicity for the human population [*28*].

A week later, the American Cancer Society issued a statement urging regulatory agencies "to set appropriate standards to minimize occupational and public exposure to the chemical, its industrial products and applications" (*29*).

On 10 February 1982, Todhunter, EPA Assistant Administrator for Pesticides and Toxic Substances, formally recommended against considering formaldehyde as a priority candidate for regulation. Characterizing formaldehyde as a "potential animal carcinogen" he observed that concern about human carcinogenicity should be "tempered" by the observations that

> quantitative and possibly qualitative results of exposure to formaldehyde appear to depend highly on exposure level, species, and route; that rats seem to be particularly sensitive to formaldehyde; and that long human experience does not seem to indicate any pressing concerns . . . [*6*].

By contrast, the CPSC voted on 22 February 1982 to ban urea-formaldehyde foam insulation (*30*). Canada and the states of Massachusetts and Connecticut had previously banned the use of urea-formaldehyde foam (*31*).

Validity of the Data

Questions have been raised about the validity of the animal data (*26*). However, the CIIT study (*13*) was rigorously peer-reviewed and is considered to be valid (*14*, *15*, *27*, *32*).

The possibility of a viral respiratory infection confounding the data in the CIIT study was considered unlikely in the NTP and Mount Sinai reports (*14*, *15*). Control animals had also shown signs of viral infection but did not develop tumors. Further, in some of the rats, nasal cancers had formed by the time respiratory viral infection occurred (*33*). In the NYU study confirming the CIIT findings, a sample of the animals was tested for the virus and found to be negative (*34*); in the CIIT study mice were not affected by the virus yet they developed tumors. Although it is unlikely that the transient viral infection contributed to the carcinogenic response of formaldehyde, people exposed to the chemical may also experience viral infections of the upper respiratory tract (*14*, *15*). Addressing the criticism that the CIIT study is flawed because "ulcerative inflammatory lesions" were present in nasal mucosa, CPSC staff scientists have written that pathologists who examined the slides from the CIIT study did not observe such changes (*35*).

The NYU studies provide confirmation of the CIIT results in a different strain of rats (*16*, *17*). According to Upton (*17*), the studies "provide decisive confirmation of the Chemical Industry Institute of Toxicology findings that formaldehyde induces squamous cell carcinoma in rats." Partly because the type of tumor was not that associated with bis(chloromethyl)ether (BCME), it is judged unlikely that the formation of BCME as a result of combination of formaldehyde and HCl was responsible for the excess squamous carcinomas in the nasal cavities (*9*, *14*, *36*). The fact that formaldehyde alone produced about the same number of tumors as when combined with HCl also argues against an etiologic role for BCME.

The prior reports of negative results in three long-term inhalation studies of formaldehyde do not detract from the significance of the CIIT and NYU studies. According to the NTP report (*14*), all three had shortcomings in experimental protocols and execution (for example, high mortality, inadequate exposure, or deficient histopathology). Bioassays in which other routes of exposure were used have been similarly limited; however, some give definite clues that formaldehyde may be carcinogenic to a variety of target tissues and animal species (*14*).

Formaldehyde Data in the Context of Established Cancer Policies

A number of principles have been elaborated in reports written during the last 10 years by various scientific committees concerning the assessment of human risk from environmental carcinogens. Composed of scientists affiliated with academic institutions, industry, and government, these committees were broadly representative of the scientific community. Their reports included those of the National Cancer Advisory Board, the Interagency Regulatory Liaison Group (IRLG), the National Research Council (NRC), the Food Safety Council, the Office of Technology Assessment (*1*), and the Occupational Safety and Health Administration (OSHA) as well as publications by the IARC and the

New York Academy of Sciences (*37–45*). Developed cooperatively by representatives of all federal agencies concerned with toxic substances control, the IRLG guidelines were based on an extensive review of the scientific literature on carcinogen assessment. EPA formally adopted (in 1979) the IRLG policy for purposes of evaluating evidence regarding suspect carcinogens as a supplement to its own Interim Guidelines for Carcinogenic Risk Assessment (*46, 47*). In particular, the report of the Toxic Substances Strategy Committee (TSSC) published in 1980 is significant because it was based on a review of 23 major reports written between 1956 and 1979 (*48*). The TSSC, composed of representatives from federal agencies with responsibility for controlling toxic substances, identified "principles and technical considerations underlying federal policies for the identification of potential human carcinogens":

> Although they have been the subject of considerable public misunderstanding, these principles are widely supported in the scientific community and in the deliberations of rulemaking and adjudicatory bodies, the courts, expert committees, and international agencies [*48*, p. 125].

Even more recently, the Office of Technology Assessment has reviewed and reaffirmed the basic principles of carcinogenicity assessment (*1*). These principles are as follows.

1) Animal testing data from properly designed and well-conducted tests are adequate for concluding that a chemical substance is a likely carcinogen in humans.

Over 30 chemicals or industrial processes are judged by the IARC to be carcinogenic or probably carcinogenic to humans on the basis of epidemiological evidence (*49*). Of those for which animal data exist, all (with two possible exceptions) have been positive in experimental animals. The two possible exceptions are benzene and arsenic. However, there is evidence from two recent bioassays that benzene is carcinogenic in animals and that arsenic may be a cocarcinogen capable of inhibiting DNA repair (*50, 51*). Hence, the IARC has concluded:

> In the absence of adequate data on humans, it is reasonable, for practical purposes, to regard such chemicals [for which there is sufficient evidence of carcinogenicity in animals] as if they presented a carcinogenic risk for humans [*52*, p. 14].

Thus:

> All Federal agencies accept a positive bioassay result in a single species as evidence that the substance is a potential human carcinogen [*1*, p. 13].

a) Animal testing at high dose levels is a valid and necessary procedure for identifying potential human carcinogens.

> The exposure of experimental animals to toxic agents in high doses is a necessary and valid method of discovering possible carcinogenic hazards in man [*39*, p. 7].
>
> Since carcinogenic response is usually dose related, the biological and statistical sensitivity of a bioassay may be enhanced by increasing the exposure levels of the test substances rather than the less feasible alternative of increasing the number of test animals to match the human population at risk [*42*, p. 5093].
>
> The basis for such extreme doses, most simply stated, is to maximize the sensitivity of the test and its capability of detecting irreversible molecular events leading to neoplastic transformations of cells which could also occur as the result of low level exposure [*40*, p. 127].

This method is valid as well as practical and necessary because

> The intrinsic carcinogenicity of a chemical does not depend on dose level although the proportion of animals developing cancers and the earliest time that tumors are detected are usually related to dosage [*48*, p. 131].

Therefore, were environmental levels considerably lower than animal dose levels, this would not invalidate the results of the testing for purposes of human risk assessment. However, in the case of formaldehyde, OTS staff (*7*), the Mount Sinai committee (*15*), and the NTP panel (*14*) have all pointed out that the tumors have occurred in rats at levels comparable to those encountered by humans.

b) Results in laboratory animals are qualitatively relevant to humans since the overall patterns of metabolism are generally similar, although the type and site of cancer induced may differ.

> Basic biological processes of those molecular, cellular, tissue and organ functions that control life are strikingly similar from one mammalian species to another [*50*, p. 85].
>
> . . . [M]etabolic studies have shown that most differences between humans and experimental animals are quantitative rather than qualitative and support the idea that animal results can be used to predict human responses [*1*, p. 126].

For example, the large body of information on the metabolism of benzo[*a*]pyrene shows that the overall pattern of metabolism in all species and systems tested is the same (although the carcinogenic potency may differ) (*53*). It should be noted that several scientific panels have raised the possibility that humans may, in fact, be more vulnerable to certain carcinogenic substances than laboratory animals (*39, 50, 51*). Weighing the usefulness of metabolic studies in human risk assessment, OSHA concluded:

> [I]n general, for the purposes of negating the identification or classification of potential occupational carcinogens, information on metabolism and pharmacokinetics is of extremely little practical value at the present time [*42*, p. 5158].

There is also scientific consensus that a negative human effect cannot be concluded from evidence that the target of the carcinogen differs in humans from that in experimental animals. In experimental carcinogenesis, the type and site of cancer seen may or may not be the same as that recorded in human studies. For example, 2-naphthylamine induces bladder cancer in man, monkeys, dogs, and hamsters but hepatic cancer in the rat (*43*).

> Present knowledge indicates that . . . the responsive target tissues or organs and the types of tumors induced in different species may vary greatly. Therefore . . . the finding of negative results in some other species generally does not detract from the validity of a positive result as evidence of carcinogenicity for the test substance [*38*, p. 39866].

Specifically, as regards formaldehyde, the CPSC states:

> There is no evidence of biological differences between the laboratory animals tested and humans that would decrease the potential for humans to develop cancer when exposed to formaldehyde [*35*].

This is in agreement with the findings of the OTS staff and the NTP panel, that formaldehyde metabolism and its reaction with cellular components is qualitatively the same in all mammalian species examined to date, including man (*7, 14*). The reports also concurred that, although formaldehyde caused nasal cancer in rats, this may not necessarily be the site affected in human beings.

(2) It is not now possible to extrapolate from animal data a "safe" population threshold for any carcinogen regardless of the mechanism of action.

> [The] position that there is no presently acceptable way to reliably determine a threshold for a carcinogen for any given population is amply supported by the evidence presented and also represents, to a large extent, a consensus of scientific opinion [*42*, p. 5137].
>
> Methods do not now exist for determining a safe threshold level of exposure to carcinogens. The major obstacle to determining whether there are safe threshold exposure levels for carcinogens is the lack of data on the effects of low exposure levels. . . . Because there is not definitive evidence of the existence of thresholds and because not all cancer variables have been identified, prudence requires that no safe level thresholds be assumed to exist. . . . Exposure to any amount of a carcinogen, however small, must be regarded as an addition to the total carcinogenic risk [*48*, pp. 133–134].
>
> The self replicating nature of cancer, the multiplicity of causative factors to which indi-

viduals can be exposed, the additive and possible synergistic combination of effects, and the wide range of individual susceptibilities work together in making it currently unreliable to predict a threshold below which human population exposure to a carcinogen has no effect on cancer risk [*38*, p. 39876].

. . . [I]t is generally accepted that a population threshold which would define a "risk-free" dose for a group of people composed of diverse individuals, if it exists, cannot now be demonstrated [*1*, p. 12].

This principle applies to any agent that contributes to the carcinogenic process:

[I]t would not be practicable or justifiable to establish different criteria for the identification, classification, or regulation of initiating and promoting agents. OSHA agrees with the NCAB Subcommittee that "any factor or combination of factors which increases the risk of cancer in humans is of concern regardless of the mechanism of action" [*42*, p. 5152].

The mechanisms by which individual carcinogens induce tumors are not easily understood. Even where it may be possible to definitively classify a substance or agent as an initiator, promoter, or complete carcinogen, these distinctions are not practically useful for purposes of regulation. This is because of the impossibility of identifying "population" thresholds for any carcinogen regardless of the mechanism by which it operates. Under defined experimental conditions, a given substance may appear to show a threshold level (that is, a dose level below which it does not increase tumor incidence). However, as indicated by a large-scale bioassay in which a threshold could not be identified for acetylaminofluorine (*54*), such observed thresholds may simply reflect the limited ability of the test system to detect effects at low dose levels. Even where experimental thresholds could be established with certainty, it would be impossible with current information and methods reliably to predict from experimental data the threshold level in humans (*55*). Such predictions are precluded by the difficulty of obtaining quantitative data at very low dose levels in small numbers of animals, variations in human host responses, and possible additive or synergistic effects of other agents that individuals might be exposed to. Thus, regulatory agencies have sought to reduce human exposure to carcinogenic substances to the lowest possible level consistent with relevant social and economic considerations.

From the above discussion it is clearly not necessary that the mechanism of action be definitively established before formaldehyde is identified as a carcinogen. However, the Formaldehyde Institute (*26*) contends that formaldehyde is likely to act primarily via an epigenetic mechanism—causing tumors only at high doses through its cytotoxic or irritant action—and is therefore probably a "threshold" carcinogen. This view is also implied in the Todhunter memorandum (*6*). The epigenetic mechanisms suggested include (i) cell destruction and rapid cell proliferation triggered at high dose levels that prevent DNA repair and detoxification systems from operating effectively and (ii) induction of ulceration, irreversible hyperplasia, or metaplasia only at high dose levels which are premalignant in themselves or serve to promote tumor formation (*6*, *26*).

The OTS, the NTP panel, and CPSC staff have rejected this interpretation, citing the substantial body of evidence that shows formaldehyde to be genotoxic and the absence of factual support for the epigenetic or "threshold" theory (*7*, *14*, *56*). While the promoting effect of formaldehyde may play a part in its overall carcinogenicity, formaldehyde is a potent alkylating agent (*57*); is a mutagen in a wide variety of test systems including microbial, insect, and mammalian systems (*8*); induces sister chromatid exchange in human lymphocytes (*58*); and causes unscheduled DNA repair in HeLa cells (*59*). Formaldehyde is able both to transform mammalian cells in culture at low concentrations and to initiate cell transformation in vitro (*60*, *61*). Formaldehyde also enhances the genotoxic effect of peroxides and radiation (*14*). Thus, with regard to the hypothesis that the "carcinogenic effects of formaldehyde are indirect, termed epigenetic," OTS concluded, "There is . . . absolutely no scientific evidence for this hypothesis in the published literature" (*7*, p. A-6).

The NTP panel further noted that "a number of agents were reported to induce epithelial hyperplasia in several types of tissues but they had no carcinogenic or tumor promoting activity associated with them" (*14*, p. 34). The panel "found no evidence that the induction of irritation or, more specifically, of epithelial hyperplasia is a sufficient condition for the carcinogenic activity of an agent" (*14*, p. 34). The NYU studies (*17*) support the NTP panel on this point. If severe irritation and resultant rapid cell turnover were either a sufficient condition or a necessary prerequisite for carcinogenicity of formaldehyde, one would expect an increased effect in animals exposed to a combination of formaldehyde and a strong irritant. However, in the NYU study HCHO and HCl were administered singly and in combination: there was no increased response to the combination of agents although HCl is a gaseous irritant; nor did HCl alone cause tumors although it did induce hyperplasia (*16*, *62*).

Scientists from the CPSC responded to the Todhunter memorandum, citing evidence against the "threshold" theories above and rejecting the assertion that the observation of endogenous levels of formaldehyde in animals without spontaneous tumors indicated a threshold (*63*). They reaffirmed their prior conclusion that "there is no evidence demonstrating that there is a threshold for formaldehyde, or a dose level below which it is certain that formaldehyde will not cause cancer" (*35*).

(3) Positive human data are not necessary to regard an agent as a likely human carcinogen warranting protective action.

Although epidemiological evidence is a necessary prerequisite to actually calling a substance a "human carcinogen," this is a point of terminology rather than a criterion for taking protective action. The most powerful reason is that the usefulness of epidemiology for the identification of carcinogens is limited by a number of constraints. These include cost, the usual long lag between exposure and appearance of cancer, the confounding effect of multiple exposures to carcinogens, and difficulties in identifying an appropriate control group [see (*48*, pp. 125–128)]. A practical problem is that very large samples must be compared if the risk in the unexposed population is low and the number expected to show the effect is small. Because of the possibility of a false negative result, the absence of positive results cannot prove an absence of risk; however, an absence of positive results may be useful in placing upper bounds on the magnitude of the risk (*64*):

. . . [N]egative epidemiological data, questionable because of limitations in the power of detection of such studies, do not deny the conclusion of carcinogenicity on the basis of animal assays [*38*, p. 39871].

Thus:

When a toxic substance is identified in a mammalian test system (in which the criteria listed in the standards are used) as a prudent health policy matter this substance is to be treated as posing a carcinogenic risk to human beings. . . . Because public policy mandates preventive health care, waiting for epidemiologic data is unacceptable, since it means waiting to "count dead bodies" [*41*, pp. 14–16].

Specifically, as regards formaldehyde: epidemiological studies completed to date have not been specifically designed to evaluate the carcinogenicity of formaldehyde in human populations; thus they

have been inconclusive or suggestive of a positive effect rather than negative regarding the carcinogenicity of formaldehyde.

These studies are inconclusive, because of small study size (the three studies together cover fewer than 2,000 deaths), poor documentation of exposure, possible multiple exposures, and study design limitations [7, p. 17].

Epidemiological studies conducted to date do not permit a definitive evaluation of the carcinogenic risk of formaldehyde to humans [9, p. 4].

Citing the conclusions of the NTP panel, CPSC stated:

The epidemiological studies presented at the CIIT conference and by the Formaldehyde Institute do not have sufficient information to be considered conclusive because of the small population size, lack of exposure data, and other confounding factors [35, p. 88].

As IARC has noted, three proportional mortality studies of workers exposed to formaldehyde had only very limited (7 to 12 percent) power to detect a threefold excess of mortality from nasal cancer (27). However, a number of studies have been suggestive of an increased cancer risk (19, 36, 65).

The preliminary epidemiological findings suggest that persons occupationally exposed to formaldehyde may experience elevated risks for certain cancers, notably of the pharynx, oral cavity, lymphatic and hematopoietic system, brain and skin [65, p. 8].

Recently, there have been several reports of rare nasal tumors in workers exposed to formaldehyde (66, 67).

According to the OTS, "because of inherent limitations, studies in progress are not likely to resolve present concerns about formaldehyde safety" (7, p. 17). This is true of an ongoing NCI study that will not be completed for at least 2 years (68). "Analysis of the design of the study . . . suggests that it may not be powerful enough to assure that formaldehyde is not carcinogenic in humans" (7, p. 27).

In summary, the IARC has evaluated the laboratory and epidemiological data on formaldehyde gas and has stated: "There is sufficient evidence that formaldehyde gas is carcinogenic to rats. Epidemiologic studies provide inadequate evidence to assess the carcinogenicity of formaldehyde to man." In accordance with its established policy (52) therefore, the working group concluded that in the absence of adequate epidemiological data, formaldehyde gas should be considered, for practical purposes, as if it represented a carcinogenic risk to man (27, p. 50).

Conclusion

Over several decades, the results of scientific research have led to policies for assessing carcinogens that have been widely endorsed by the scientific community and accepted by regulatory agencies in this country and abroad. These policies are based on the principles that valid positive animal data are presumptive evidence of carcinogenicity in humans and that population thresholds cannot be identified for carcinogenic substances. These two principles are the heart of present federal programs to protect human health from cancer-causing chemicals, and are consistent with accepted social policy that makes a conscious decision to err on the side of caution in addressing health risks. The present behavior of two U.S. regulatory agencies regarding formaldehyde suggests that they are disregarding the substantial evidence and rationale on which the established policies relating to assessment and regulation of carcinogens have been based. Indeed, it appears that EPA is informally revising its cancer policy to decrease reliance on animal studies—a step that could have the effect of substantially delaying or indeed barring altogether protective action on substances such as formaldehyde, pending the development of positive epidemiological data.

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APPENDIX E

ASSESSMENT OF TECHNOLOGIES FOR DETERMINING CANCER RISKS FROM THE ENVIRONMENT

JUNE 1981

OTA Reports are the principal documentation of formal assessment projects. These projects are approved in advance by the Technology Assessment Board. At the conclusion of a project, the Board has the opportunity to review the report but its release does not necessarily imply endorsement of the results by the Board or its individual members.

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INITIATION, PROMOTION, AND SYNERGISM

Cancer causation is thought to involve at least two steps: an early initiation step and a later promotion effect. A single agent may cause both events, or two or more separate agents working in the proper sequence may be necessary. Initiation is generally thought to involve a genetic change in the cell, but that change is not expressed and does not result in a tumor unless a promotion event follows it. The latent period of most cancers—the time between exposure to an initiator and appearance of the disease—is often 20 years or more. This long latent period is the cause of a great deal of apprehension among policymakers, scientists, and the general public because new substances and living habits are continually introduced, and today's harmful exposures may not cause ill effects for years.

The time between exposure to a promoter, after initiation has occurred, and the appearance of cancer, can be much shorter. "Initiated cells" may lie quiescent if they are not "turned on" by a promoter, and cancer may never develop if sufficient exposures to promoters do not occur. The practical importance of this property of promoters is illustrated by the change in cancer risk experienced by exsmokers of cigarettes. Smoking is thought to play both an initiation and promotion role in cancer causation. Because of smoking's promotional properties, the risk of cancer falls off rapidly after a smoker quits.

Synergism, another form of interaction, occurs when two or more substances potentiate each other's effects, producing more cancers than can be accounted for by adding the effects of each. The multiplicative effects of cigarette smoking and exposure to asbestos and smoking and exposure to radiation are well-known examples of synergism.

Unfortunately, relatively little is understood about interacting agents—either synergisms or initiation and promotion. In particular, promoters have not received as much experimental attention as have initiators or complete carcinogens, which both initiate and promote.

FACTORS ASSOCIATED WITH CANCER

The possibility that cancers may be prevented by eliminating or modifying behaviors or exposures has stimulated the continued search for factors important in cancer causation. Importantly for prevention efforts, studies of agents that interact in causing cancer have shown that altering exposure to a single factor may eliminate or greatly reduce the risk of cancer.

Evidence for the associations between various "factors" and cancer ranges from very strong to very weak. Regardless of the strength of the association, the estimated magnitude of the amount of cancer associated with factors also varies. For instance, the strongest associations include those between smoking tobacco and respiratory cancers, between asbestos and cancer of the lung and other sites, and between ionizing radiation and cancer at many sites. While each of the three associations is strong, the percentage of cancer associated with each is different. Smoking is associated with more than 20 percent of cancer, asbestos with between 3 and 18 percent, and natural radiation with less than 1 to 3 percent.

Table 2 (pp. 8-9) presents information about associations between several factors and cancer. The associations between some aspects of human biology and reproduction and a proportion of cancer, especially in women, are well-established, as is the association of a small percentage of cancer with medical drugs. The specifics of the association between human diet and cancer are not understood, but diet is generally considered to be associated with a large percentage of cancer. Infection, especially viral infection, is associated with particular tumors that occur mainly in people in other parts of the world, and is also thought to be associated with some urogenital cancers in the United States.

The magnitude of associations between air and water pollution and cancer are argued and studies to examine the associations are difficult to design and execute. The same is true of associations between consumer products and cancer.

There is no disputing that occupational exposures to asbestos and some chemicals have caused human cancer, and table 2 presents estimates both for asbestos-caused cancer and total occupationally associated cancer. As the data in the table show, there is significant disagreement about how much current cancer and cancer in the near future is to be associated with occupational exposures.

Associating a high or low percentage of cancer with a factor does not reflect the present-day opportunities for prevention. For instance, diet is considered very important, but because associations with specific elements and cancer are poorly understood, there are few practical preventive measures now available.

The opportunities for prevention of occupation-related cancers at this time are better. Identification of a cancer-causing substance in the workplace can lead to reductions in exposure either by regulation or through voluntary activities on the part of industry. While reducing or eliminating occupational exposures to carcinogens might only slightly reduce the overall cancer toll, it could have a profound effect on the amount of cancer among workers who may now be at risk. A reduction of only 1 percent in cancer mortality means 4,000 fewer cancer deaths each year, so that even small reductions translate into relatively large numbers.

IDENTIFICATION OF CARCINOGENS

The Federal Government has centered efforts to control cancer on reducing exposures to chemical and physical carcinogens.

Carcinogens can be identified through epidemiology—the study of diseases and their determinants in human populations—and through various laboratory tests. Currently 18 chemicals and chemical processes are listed as human carcinogens and an additional 18 listed as probable human carcinogens by the International Agency for Research on Cancer (IARC), a World Health Organization agency. IARC conclusions, based on reviews of the worldwide literature, are accepted as authoritative by government agencies and many other organizations.

In the United States, Congress has directed the National Toxicology Program (NTP) to produce an annual list of carcinogens. The first list, published in 1980, was composed of the substances identified as human carcinogens by IARC. The next publication is to be considerably expanded and will include usage and exposure data and information on the regulatory status of over 100 chemicals either considered to be carcinogens or regulated by the Federal Government because of carcinogenicity.

Cancer epidemiology established the associations between the 36 substances and human cancer listed by IARC as well as the carcinogenicity of smoking, alcohol consumption, and radiation. However, epidemiology is limited as a technique for identifying carcinogens because cancers typically appear years or decades after exposure. If a carcinogen were identified 20 years after its widespread use began, many people might develop cancer from it even though its use is then immediately discontinued. Certainly, those people who were identified in the study as having had their cancer caused by the substance would have been irreparably harmed. Epidemiology is complicated because people are difficult to study; people move from place to place, change their type of work, change their habits, and it is hard to locate them and to estimate their past exposures to suspect agents.

Laboratory tests, which do not depend on human illness and death to produce data, have been developed to identify carcinogens. Currently, the testing of suspect chemicals in laboratory animals, generally rats and mice, is the backbone of carcinogen identification. The suspect chemical is administered to the animals

Table 2.—Summary of Cancer-Associated Environmental Factors[a]—Continued

Factor[b]	Sites considered in drawing the estimates	Range of estimates associated with factor
Natural radiation	***Skin, breast, thyroid, lung, bone, blood (leukemia)***	***Less than 1-3 percent***
There is no doubt that natural radiation, consisting of ionizing radiation from cosmic rays and radioactive materials, can cause cancer. While disagreements persist regarding the amount of risk associated with low-level ionizing radiation, the estimates generally agree within one order of magnitude. Ultraviolet radiation from the Sun is believed responsible for most of the 400,000 nonmelanoma skin cancers. These tumors are not usually included in quantitative estimates of cancer rates because they are poorly recorded and generally curable. They are not included here.		
Consumer products	***Possibly all sites***	***Less than 1-2 percent***
Substances known to be carcinogenic are present in consumer products at usually very low levels. The extent to which they contribute to the overall cancer rate is uncertain.		
Unknown associations	***All sites***	***(?)***
Many substances have not been tested for carcinogenicity and associations between some of those substances and cancer may exist. Furthermore, substances newly introduced into the environment may have an impact in the future. In particular, there is concern that point sources of pollutants, such as dumps, may be contributing to cancer. Because the associations are unknown, the estimate is uncertain but it is certainly not zero. Additionally, stress, which may be manifested by overeating, smoking, or in other ways, probably plays a role in cancer causation.		

[a]Many cancers may be associated with more than one factor. Factors are not mutually exclusive, and the total, if all associations were known, would add to much more than 100 percent.
[b]Estimates are listed under the factors that most closely approximate the description published with them. The estimates are detailed and their sources referenced in ch. 3.
[c]Range of single estimate.
SOURCE: Office of Technology Assessment

either in their food, water, air, or (less frequently) by force feeding, skin painting, or injection. As the animals die, or when the survivors are killed at the end of the exposure period (which is generally the lifespan of the animal), a pathologist examines them for tumors. The number of tumors in the exposed animals is then compared with the number in a group of "control" animals. The controls are treated exactly as the experimentals except that they are not exposed to the chemical under test. The finding of a significant excess of tumors in the exposed animals compared with the number found in controls in a well-designed, well-executed animal test for carcinogenicity leads to a conclusion that the chemical is a carcinogen in that species.

IARC has reviewed the literature concerning 362 substances which have been tested in animals and considers the data "sufficient" to conclude that 121 are carcinogens. For about 100 others, there was "limited" evidence of carcinogenicity, indicating that further information is desirable, but that the available evidence produces a strong warning about carcinogenicity. Data were "insufficient" to make decisions about the carcinogenicity of the remaining substances. The IARC review program is active and continuing and updates it findings periodically.

The reliability of animal tests, bioassays, depends on their design and execution. NCI published guidelines for bioassays in 1976. Bioassays now cost between $400,000 and $1 million and require up to 5 years to complete. Clearly such expensive tools should be used only to test highly suspect chemicals, and much effort is devoted to selecting chemicals for testing.

Molecular structure analysis and examination of basic chemical and physical properties are used to make preliminary decisions about the likelihood of a chemical being a carcinogen and whether or not to test it. For instance, greater suspicion is attached to chemicals that share common features with identified carcinogens. Unfortunately, not all members of a structural class behave similarly, which places limits on this approach. In making decisions about whether chemicals should be tested further, scientists consider other data, including any available toxicological information. These preliminary decisions may be critical, because if a decision is made not to test a substance, nothing

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more may be learned about its toxicity. The wrong decision might result in a carcinogen entering the environment and being ignored until it causes disease in a large number of people.

The most exciting new developments in testing are the short-term tests, which cost from a few hundred to a few thousand dollars and require a few days to months to complete. Such tests have been under development for about 15 years, and most depend on biologically measuring interactions between the suspect chemical and the genetic material, deoxyribonucleic acid (DNA). The best-known test, the "Ames test," measures mutagenicity (capacity to cause genetic changes) in bacteria. Other short-term tests use micro-organisms, nonmammalian laboratory animals, and cultured human and animal cells. Some measure mutagenicity and some the capacity of a chemical to alter DNA metabolism or to transform a normal cell into a cell exhibiting abnormal growth characteristics.

Many chemicals that have already been identified as carcinogens or noncarcinogens in bioassays have also been assayed in short-term tests to measure congruence between the two types of tests. Results from these "validation" studies vary, but up to 90 percent of both carcinogens and noncarcinogens were correctly classified by short-term tests. These figures are sometimes questioned because they were derived from studies that excluded classes of chemicals known to be difficult to classify by the short-term tests being evaluated. However, the International Program for the Evaluation of Short-Term Tests for Carcinogenicity concluded that the Ames test, in combination with other tests, correctly identified about 80 percent of the tested carcinogens and noncarcinogens. That study purposefully included some chemicals known to be difficult to classify by short-term tests, and it further demonstrates the promise of short-term tests.

Short-term tests now play an important role in "screening" substances to aid in making decisions about whether or not to test them in animals. The role of short-term tests is expected to increase in the future as more such tests are developed and validated. However, the eventual replacement of animal tests by short-term tests is probably some time away.

One factor likely to retard replacement of animal tests by short-term tests is the poor quantitative agreement between the two kinds of tests. Qualitative agreement, as measured in validation studies, is good—i.e., a mutagen is very likely to be a carcinogen—but poor quantitative agreement means that a powerful mutagen may be a weak carcinogen or the other way around. Additionally, because there is some evidence to support the idea that the potency of a carcinogen in animals is predictive of its potency in humans, the poor agreement about potency between animal and short-term tests may inhibit wider use of the latter tests.

PROGRAMS TO IDENTIFY CARCINOGENS

Government Programs

The most important recent development in governmental management of test development and implementation is the establishment of NTP by the Department of Health, Education, and Welfare in 1978. The program encompasses the short-term and bioassay testing activities of the Department of Health and Human Services (DHHS) but not the testing programs that exist in other executive branch departments. Other agencies with a stake in carcinogen testing, the Environmental Protection Agency (EPA), the Consumer Product Safety Commission (CPSC), and the Occupational Safety and Health Administration (OSHA), participate in the selection of substances to be tested by NTP. Each of these agencies retains responsibility for development of policies and guidelines for testing and interpretation of results under the laws that they administer.

NTP has assumed the management of the carcinogen bioassay program that was formerly located at NCI. This is the largest single test program, and began the testing of about 50 chemi-

cals in fiscal year 1980; the number will drop to about 30 in fiscal year 1981 because of budgetary limitations.

Government-sponsored cancer epidemiology is supported principally by the National Institutes of Health, with the National Institute of Occupational Safety and Health, and other agencies carrying out some research. Epidemiologic research is marked by flexibility in experimental design, and it has not been placed under an umbrella organization like NTP.

Nongovernment Programs

Many chemical, drug, and petroleum companies have large, active, inhouse toxicology and epidemiology units. These resources are employed to develop information about substances of concern to the companies and also to supply data to Federal regulatory agencies. One of the most modern toxicology laboratories is that of the Chemical Industry Institute of Toxicology (CIIT). This laboratory recently completed extensive testing of formaldehyde, which demonstrated that the chemical causes nasal cancer in rats. CPSC and other agencies have proposed regulations to curtail exposures to formaldehyde based on information from CIIT studies.

Many epidemiologic studies and much of the development of test procedures take place in academic institutions. Funding for these activities comes from both Federal and non-Federal sources, and these institutions have been important in gaining knowledge and improving techniques.

ANALYSES OF TEST RESULTS

Results from tests are conveniently discussed as being "positive," "negative," or "inconclusive." A "positive" test is sufficient to convince all (or most) experts that the tested substance causes the measured effect—e.g., cancer in bioassay. Similarly, a "negative" result is one that convinces all (or most) experts that the tested substance does not exert the effect measured in the test. "Inconclusive" means that no conclusion can be drawn from the test. Test results are analyzed initially by the scientists who conduct the tests. Their conclusions may be reviewed by other experts later on, and such peer review is important for the acceptance or rejection of the conclusions.

Positive epidemiologic results show an association between an exposure or behavior and human cancer. When they are available and based on a valid study, they tend to dominate any decision to be made about carcinogenicity. When no or limited epidemiologic data are available, bioassays which measure carcinogenicity in intact animals are the most important source of information. The last decade saw Government organizations, Congress, executive agencies, and the courts, as well as private sector organizations endorse bioassays and agree that they can be used to identify potential human carcinogens. For instance, IARC concluded:

> . . . it is reasonable, for practical purposes, to regard chemicals for which there is sufficient evidence of carcinogenicity . . . in animals as if they presented a carcinogenic risk for humans.

The use of short-term test results varies depending on whether the substance being tested is *in use* or *new*. When making decisions about currently used chemicals, short-term test results are used to decide whether or not to proceed to a bioassay, and they are accorded a supporting role in making decisions about carcinogenicity.

In industry, short-term tests play a role in making decisions about whether or not to proceed with *development* of a new chemical. A positive result, indicating that the cost of developing the chemical for market might have to include extensive and expensive toxicological testing, may be factored into a manufacturer's decision to develop or not to develop a chemical. A risky chemical may be dropped from consideration for further development.

A problem that bedevils decisionmaking is the existence of both "positive" and "negative" results from tests of the same substance. Careful analysis of the design and execution of the "pos-

itive" and "negative" tests sometimes resolves the discrepancies and allows reconciliation of the results. When the conflicting results cannot be explained, more importance is attached to the positive results.

It is not possible to say how many of the 55,000 chemicals in commerce are carcinogens. About 7,000 have been tested in bioassay, and 10 to 16 percent were "positive." However, this percentage has little meaning when discussing all chemicals. There is a strong bias toward testing risky chemicals, as is shown by the fact that about half of 190 chemicals tested in NCI's bioassay program were reported to be positive. On the other hand, many tests done years ago are insensitive by today's standards and that would tend to decrease the percentage of substances detected as carcinogens.

The IARC list of 18 human carcinogens, plus tobacco smoke, alcohol, radiation, and the 18 probable human carcinogens, provide a minimal answer to the question of how many substances are known to cause or probably cause human cancer. The IARC list of 121 substances that produced "sufficient" evidence for carcinogenicity in animals expands the number of substances that must be considered as carcinogenic hazards for humans. These two lists add up to the "rock-bottom" number of about 160 substances. How many more carcinogens will be identified is uncertain, and what is known about the tested chemicals may be overshadowed by what is unknown both about untested chemicals and about complex human exposures and behaviors that are not amenable to laboratory testing.

EXTRAPOLATION FROM TEST RESULTS TO ESTIMATES OF HUMAN CANCER INCIDENCE

Extrapolation techniques are used to estimate the probability of human cancer from study-derived data. Extrapolation can be divided into two parts. "Biologic extrapolation" involves the use of scaling factors to make adjustments between biologic effects in small, short-lived laboratory animals and in humans. "Numeric extrapolation" models are used to estimate the probability of cancer at doses below those administered to animals in a test and to estimate cancer incidence at exposure levels other than those measured in epidemiologic studies.

Some extrapolation models assume a "threshold" dose, a nonzero dose below which exposures are "safe" and not associated with risk. Individual thresholds may exist, because not all individuals exposed to similar levels of carcinogens develop cancer, but such differences in sensitivity may also be explained by differences in luck rather than in biology. However, it is generally accepted that a population threshold which would define a "risk-free" dose for a group of people composed of diverse individuals, if it exists, cannot now be demonstrated. Federal agencies do not accept the idea of thresholds in making decisions about carcinogenic risks.

Numeric extrapolation models differ in the incidence of cancer that they predict from a given exposure. Extrapolation models which assume that incidence at low-exposure levels is directly proportional to dose generally estimate higher incidences. Such "linear" models are "conservative" in that, if they err, they overestimate the amount of disease to be expected. All governmental agencies that use extrapolation employ linear models for predicting cancer incidence. Other models project risks that decrease more rapidly than dose, and they are advanced as alternatives to the linear model. The choice of a model is important because, if an acceptable level of risk were decided on, almost any other model would allow higher exposures than do linear models.

Opinions differ about whether and how extrapolation methods should be used in estimating the amount of human cancer that might be caused by exposure to a carcinogen:

- Some individuals object to any use of numeric extrapolation. For them, identification of a substance as a carcinogen is enough to justify efforts to reduce or to eliminate exposure.
- Other people see extrapolation as useful to separate more risky from less risky substances.
- The most extensive use of extrapolation is recommended by people who urge that extrapolation methods be used to estimate quantitatively the amount of human cancer likely to result from exposures. Such estimates are seen as necessary by those who wish to compare quantitatively the risks and benefits from carcinogens.

The disagreements among the groups who hold different opinions about use of extrapolation are vocal and current. A particular problem in quantitative extrapolation arises from the fact that different extrapolation models produce estimates of cancer incidence that differ by factors of 1,000 or more at levels of human exposure. Given such uncertainty, some labor and environmental organizations and many individuals refuse to choose one model or another for estimating the impact of a carcinogen on humans, and oppose the use of quantitative extrapolation. Fewer objections are raised against choosing a model to order carcinogens on the basis of their likelihood of causing cancer. Regardless of which particular model is chosen, it should produce approximately the same relative ranking as any other.

Proponents of quantitative extrapolation argue that careful attention to the available data aids in choosing the correct model and reduces chances for error. Arguments about the applicability of these techniques will continue, especially because efforts to apply cost-benefit analysis to making decisions about carcinogens will require quantitative estimates of cancer incidence.

There are now no convincing data to dictate which extrapolation model is best for estimating human cancer incidence, whether from epidemiologic data or animal data, or even that one model will be consistently better than all others. However, one particular model for estimating human incidence from animal data (linear, no threshold extrapolation and relating animal and humans on the basis of total lifetime exposure divided by body weight) has been reported to estimate human cancer incidence within a factor of 10 to 100 when compared to incidence measured by epidemiologic studies. While this agreement is gratifyingly good, data exist to make these comparisons for fewer than 20 substances.

STATUTORY AND REGULATORY DEFINITIONS OF "CARCINOGEN"

Regulation of carcinogens has been marked by repeated arguments about the amount and kind of evidence necessary to make decisions to regulate substances as carcinogens. Several Federal documents describe the types of tests agencies will consider and the criteria they will apply to make such decisions. Statements of regulatory agency policy are found in EPA's Interim Guideline for Carcinogenic Risk Assessment, EPA's air carcinogen policy statement, OSHA's generic cancer policy, and the Regulatory Council's policy statement, which drew heavily on recommendations of the Interagency Regulatory Liaison Group (IRLG). IRLG now coordinates Federal regulatory agency discussion about identifying and characterizing toxic substances, including carcinogens.

All Federal agencies accept positive epidemiologic studies as strong evidence for carcinogenicity, and a positive bioassay result in a single species as evidence that the substance is a potential human carcinogen. All relegate short-term tests to a supporting role. Trade associa-

4. Methods for Detecting and Identifying Carcinogens

Beginning with this chapter, the focus of this report shifts from all causes of cancer to only chemicals. This shift does not represent a decision that chemicals, in the workplace or in the general environment, are more important in cancer causation than dietary elements, personal habits, radiation, or certain aspects of human biology. However, it does reflect the major legislative and regulatory emphasis recently placed on chemicals, and the greater ease with which chemical carcinogens can be detected by present-day methods.

Different methods are available, employing different techniques, using different test organisms, and producing different types of information about carcinogenicity. This chapter discusses a variety of those methods, their strengths and weaknesses, some results from each, and the tools they require.

METHODS

There are four major methods for detecting and identifying carcinogens:

1. molecular structure analysis,
2. short-term tests,
3. long-term chronic bioassays in laboratory animals (termed "bioassays" or "animal tests" hereafter), and
4. epidemiology.

The first two methods produce information about potential carcinogenicity; the third provides direct evidence of carcinogenicity in animals; the fourth produces direct evidence about cancer in man. These categories are briefly described in table 23.

Probably no statement made in the last column of table 23 is free from dispute. Results may be, and frequently are, challenged for several reasons: because the test was incorrectly designed or executed (all methods); because the method does not directly measure carcinogenicity (methods 1 and 2); because the test is too sensitive and produces false positives (methods 2 and 3); because the test is too insensitive and produces false negatives (method 4); and because the test does not measure human experience (all methods but 4), etc.

Knowledge about tests and about the validity of test results increases as the tests are more often used, more discussed, and more refined. The state of scientific knowledge plays an important role in decisions to test or not to test a chemical, decisions about which tests are appropriate, and decisions about interpretation of the test results. As will be discussed, "policy statements," sometimes issued as guidelines or standards, detail the methods that an organization will use in making decisions. A certain tension is apparent in all the policies. Tests cost money and take time; bigger and better tests cost more and take more time; compromises are necessary in the design of each test so that a reasonable number of chemicals can be tested.

An equally important issue is the amount of information necessary to decide that a chemical is or is not a carcinogen that requires some control action. The fact that some regulations are based on nonhuman test systems shows that proof that a chemical is a human carcinogen is not demanded. This illustrates that prevention of cancer is seen as so important that it is appropriate to make decisions to restrict exposures before human damage is observed.

ards (106) and Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guidelines (102) accept short-term tests as measures for mutagenicity but do not consider them in making decisions about carcinogenicity. However, they mention that test developments are promising.

An important step in making decisions about the use of short-term tests are the ongoing validation studies which compare predictions made from short-term tests to knowledge about carcinogenicity from bioassays or epidemiology. These studies, although limited by the quality and quantity of data about carcinogenicity, are producing valuable information. In addition, studies of molecular mechanisms of mutagenicity and carcinogenicity are important in deciding about the applicability of short-term tests.

The problem of the carcinogens that are not detected (false negatives; lack of sensitivity) and the noncarcinogens that are falsely detected (false positives; lack of specificity) by any one test might be solved with additional short-term tests. The great attractiveness of a battery of short-term tests is that it might correctly identify all carcinogens and noncarcinogens. Unfortunately, no such battery has yet been defined. The composition of the battery will depend on validation studies and acceptance of each component test.

The growing use of short-term tests shows that short-term tests have moved to an important position in toxicology. The speed with which they have been incorporated into Government and private sector programs reflects the importance of the need to which they are addressed.

BIOASSAYS

Chemicals cannot be tested for carcinogenicity in humans because of ethical considerations. A substantial body of experimentally derived knowledge and the preponderance of expert opinion support the conclusion that testing of chemicals in laboratory animals provides reliable information about carcinogenicity. Animal tests employ whole mammal systems, and although they differ one from another, all mammals, including humans, share many biological features (266):

> Effects in animals, properly qualified, are applicable to man. This premise underlies all of experimental biology and medicine, but because it is continually questioned with regard to human cancer, it is desirable to point out that cancer in men and animals is strikingly similar. Virtually every form of human cancer has an experimental counterpart, and every form of multicellular organism is subject to cancer, including insects, fish, and plants. Although there are differences in susceptibility between different animal species, and between individuals of the same strain, carcinogenic chemicals will affect most test species, and there are large bodies of experimental data that indicate that exposures that are carcinogenic to animals are likely to be carcinogenic to man, and vice versa.

In comparison to short-term tests and epidemiology, bioassays have had a longer development period and enjoy greater acceptance than the short-term tests; they are more easily manipulated to produce evidence linking a particular substance to cancer than epidemiology, and they can predict human risks rather than relying on cases of human cancer to demonstrate risk. On the other hand, they take longer and cost much more than short-term tests.

The bioassay's apparent simplicity belies the difficulty of executing such experiments. Briefly, the suspect chemical is administered to a population of laboratory animals. As animals die or are killed during the course of the study, they are examined for the presence of tumors. At the end of the treatment and observation period (generally about 2 years), the surviving animals are killed and examined. A control group of animals is treated exactly the same except that they are not exposed to the suspect substance. The type and number of tumors and

other relevant pathologies present in the exposed animals are compared with those in the control group, and statistically analyzed.

A statistical expression commonly used to describe a positive result is ". . . it has a p value less than 0.05" (5 percent). The p value is the probability that the observed effect might be explained by chance; in this case, the expression means that the probability of the observed carcinogenic effect being due to chance is less than 5 percent. A p value of 0.05 or less is commonly required to decide that a test result was statistically positive.

Finally a conclusion is drawn about whether or not the evidence indicates that the substance caused cancer in the exposed animals. An excellent discussion of experimental design and analysis is available from the International Agency for Research on Cancer (IARC) (187).

The first successful experimental induction of cancer in animals (in 1915) showed that painting rabbits' ears with coal tar produced tumors which morphologically resembled human tumors associated with exposure to the same agent (cited in 342). Most chemicals which are presently known to cause cancer in humans are also carcinogens in animals.

Verification of the predictive power of bioassays would require that the agent be shown to be a human carcinogen. Currently, IARC maintains that convincing evidence for human carcinogenicity is available for only 18 exposures, including 14 chemicals. At the same time, it lists 142 substances for which data are "sufficient" to conclude that they are carcinogenic in animals. It is difficult to demonstrate human carcinogenicity. Once a substance is shown to be an animal carcinogen, regulatory restrictions on and voluntary reductions in the use of the chemical may reduce human exposures, making those demonstrations more difficult. Reductions in exposure in such cases are far more important to human health than the foregone opportunities to verify the predictive powers of bioassays.

Standard Protocols for Bioassays

An important event in bioassay design was the development of NCI's Guidelines for Carcinogenic Bioassay in Small Rodents (331). The guidelines describe minimum requirements for the design and conduct of a scientifically valid bioassay and discuss important considerations in undertaking such studies. They are written to provide flexibility in experimental design while setting certain minimal requirements:

1. Each chemical should be tested in at least two species and both sexes. Rats and mice are usually the species of choice.
2. Each bioassay should contain at least 50 animals in each experimental group. When both sexes of two species are used and two treatment levels are administered and a third group is used as controls, a total of 600 animals is needed (see table 26).
3. Exposure to the chemical should start when the animals are 6 weeks old or younger and continue for the greater part of their lifespan. Mice and rats are usually exposed for 24 months.
4. One treatment group should receive the maximum tolerated dose (MTD), which is defined as the highest dose that can be given that would not alter the animals' normal lifespan from effects other than cancer. The other treatment group is treated with a fraction of MTD.
5. The route by which a chemical is administered should be the same or as close as possible to the one by which human exposure occurs.
6. Animals are closely monitored throughout the study for signs of toxic effects and other causes affecting their health.
7. Examination of animals is conducted by or under the direction of a pathologist qualified in laboratory animal pathology.

The guidelines also specify that special procedures (e.g., organ function tests, body burden determinations, absorption and excretion tests) may be needed for evaluating certain chemicals.

Table 26.—Distribution and Number of Animals in a Typical Bioassay Study of Carcinogens

Experimental groups	Species A		Species B	
	Males	Females	Males	Females
Dosage MTD[a] group	50	50	50	50
Dosage MTD/x group	50	50	50	50
Control group	50	50	50	50

[a]Maximum tolerated dose

SOURCE: National Cancer Institute

A National Research Council report (262) suggested a two-generation bioassay when there is special concern with prenatal and perinatal effects of a substance. In the suggested two-generation experiment, the first generation is exposed from 6 weeks of age through their adult life, including periods of reproductive activity and pregnancy, and the offspring are exposed for their lifespans. The most important two-generation experiments, from the standpoint of public policy, were the three showing saccharin to be a bladder carcinogen in second generation rats (282). The advantage of the two-generation experiment is that it exposes fetuses and very young animals, which may represent the most sensitive stages of life. This procedure costs more and requires more time to complete than the one generation experiment. Probably because of those disadvantages, it has not often been used.

Table 27 compares some specifics of NCI guidelines with those proposed by EPA for testing under FIFRA (102) and TSCA (106). NCI guidelines state that at least two-dose levels be tested; EPA requires three test doses. The highest dose, high-dose level (HDL), for TSCA is defined as being "slightly toxic" and is to be determined in a 90-day-feeding study to precede the oncogenicity experiment. The other two doses are to be fractions of HDL. EPA prefers the term HDL, which is less specifically defined than MTD, because of the controversies which have erupted over defining MTD. Three-dose levels are proposed by EPA because a review of many NCI bioassays revealed that tumor incidence was sometimes higher at a dose of MTD/2 than at MTD because the higher dose killed some animals before tumors might have developed. The third-dose level will also provide additional information about the dose-response curve (102). The text which accompanies the proposed EPA guidelines for carcinogen testing under FIFRA (102) contains additional information about alternative approaches considered and subsequently discarded for the guidelines.

Three to five years are required to complete a bioassay. A subchronic test, to set dose levels, requiring 2 to 6 months, is followed by an average 24 months of exposure to the agent, and sometimes an additional 3 to 6 months observation period. Pathological examination of tissues from the animals and evaluation of the pathological and other data may take an additional year.

The cost of a bioassay has been variously estimated: NCI estimates about $400,000, TSCA guidelines (106) estimated $400,000, and EPA (112) later estimated a range from $390,000 to $980,000.

Some changes have been made in protocols since the NCI guidelines were published, but in contrast to the situation in spring 1977, when OTA reviewed carcinogen testing (282), apparently much less confusion and contention now exist about what constitutes an adequate bioassay. NCI guidelines are for minimal standards; certainly larger populations of animals can be tested. For very important bioassays, larger numbers of animals or more dosage groups might be specified.

Objections to the Usefulness of Bioassays

Some general aspects of test design are seldom disputed. Examples of such provisions are the requirement of a minimum number of animals in the test groups and that (generally) both sexes

Table 27.—Guidelines for Bioassay in Small Rodents

	NCI (331)[a]	FIFRA (102)	TSCA (106)
Endpoint	Carcinogenicity	Oncogenicity	Oncogenicity
Study plan:			
Animal species	2, rats and mice	2, rats and mice	2, rats and mice
Number of animals at each dose	50 males, 50 females	50 males, 50 females	50 males, 50 females
Dosages	2, MTD MTD/2 or MTD/4 plus no-dose control	3, MTD MTD/2 or MTD/4 MTD/4 or MTD/8 plus no-dose control	3, HDL HDL/2 or HDL/4 HDL/4 or HDL/10 plus no-dose control
Dosing regimen			
Start	At 6 weeks of age	In utero or at 6 weeks	At 6 weeks of age
End	At 24 months of age	Mice, 18-24 mos; rats, 24-30	At 24-30 months of age
Observation period	3-6 months after end of dosing	N.s.	N.s.
Organs and tissues to be examined	All animals: external and histopathologic examination (ca. 30 organs and tissues)	All animals: external examination; some animals: pathologic exam of 30 organs and tissues, other animals, fewer organs and tissues	All animals: external and histopathologic examination (ca. 30 organs and tissues)[b]
Personnel qualifications:			
Study director	N.s.	N.s.	Responsibilities detailed
Pathologist	Board-qualified	N.s.	Board-certified or equivalent
Animal husbandry	N.s.	N.s.	Board-certified vet. or equivalent
Cost estimate	N.s.	N.s.	$400,000 ± 160,000

Abbreviations: MTD, Maximum tolerated dose, causes minor acute toxicity
HDL, high dose level, causes some acute toxicity
N.s., not specified

[a] The NCI Guidelines specify the indicated minimum requirements. They allow for flexibility in experimental design so long as the minimum requirements are met.
[b] EPA estimates that the 40,000 microscope slides produced in this examination will require more than 3/4 of a year of a pathologist's time for analysis.

SOURCE: Office of Technology Assessment

be tested. On the other hand, consensus does not exist about some aspects of experimental design, for instance: How high a dose is to be administered? The policy of the agency that draws up the guidelines is reflected in what it says about the arguable aspects of experimental design. Tomatis (341) has discussed five debated issues about bioassay.

1. **Doses of chemicals to which test animals are exposed are too high and are not predictive for effects at levels of human exposure.**

High doses of suspect carcinogens are necessary to increase tumor incidence to a level that can be detected in the limited number of animals used for tests (180). A chemical causing tumors at a rate of 0.5 percent in the U.S. population would result in over 1 million cancer cases. But an incidence of 0.5 percent would very probably go undetected in the usual test population of 50 male plus 50 female rats or mice. Administration of the chemical at a 10-times higher dose might increase the response to a detectable level given comparable sensitivity between the test animals and humans. High doses are necessary to increase the sensitivity of the tests, but arguments arise over whether or not a dose is so high that it is not predictive of what happens at lower doses.

The biological argument against depending on results at high doses centers on the contention that such doses may alter metabolism or cause local irritations or other toxic response and cause cancer through a pathway that would not exist at lower doses (60,139,278). A solution sometimes offered to the problems raised by high doses is to run bioassays with many more animals tested at lower doses. The most spectacular attempt at this was the National Center for Toxicological Research (NCTR) ED_{01} study

which used 24,000 mice and was designed to detect one cancer in 100 animals. Unfortunately, neither it nor (probably) any experiment can eliminate the necessity for testing chemicals at doses significantly higher than those experienced by humans. Even 24,000 is a small number compared to the number of people exposed to many chemicals.

2. **Routes of exposure in animal tests do not correspond to routes of human exposure.**

Chemicals are administered to laboratory animals in either food, water, by inhalation, force-feeding (gavage), skin-painting, or injection. Few objections are raised to administration in food, water, or by inhalation when the chosen route mimics the route of human exposure. More objections are raised to gavage, skin-painting, injection, or ingestion when that is not the normal human exposure route. However, such methods are sometimes necessary and, furthermore, carcinogens appear to be distributed throughout the body regardless of the route of exposure. EPA (106) stipulates that "to the extent possible, route(s) of administration should be comparable to expected or known routes of human exposure." Adherence to such suggestions will reduce the frequency of this objection.

3. **Some animals used for testing are so biologically different from humans that results from them have no value.**

Choice of animals for bioassays represents a compromise. Most current guidelines require or suggest that chemicals be tested in two rodent species, generally rats and mice. The advantages of these species are their small size, reducing the space necessary for housing, short lifespans (2 to 3 years), reducing the time needed for a lifetime study, and a large amount of information about the genetics, breeding, housing, and health of these animals. Rats and mice are cheap to buy, feed, and house, as compared with larger animals.

Primates are sometimes used for certain toxicological testing. They are certainly more like humans than rodents but their supply is limited. They are expensive, live up to 25 years, and require large areas for housing. Despite these difficulties, NCI now maintains about 600 monkeys for carcinogenicity testing at a cost of about $500,000 per year (2). Dogs are thought to be between rodents and monkeys in their apparent likeness to humans, but they are more like primates in costs.

Differences in metabolism, bioaccumulation, and excretion between rodents and humans should be considered in interpreting the significance of animal results for humans. There is no question that further research in the comparative biochemistry and physiology of man and rodents is necessary, but the comparisons will ultimately be limited by restrictions on what can be determined by experimentation in humans. Moreover, metabolic studies have shown that most differences between humans and experimental animals are quantitative rather than qualitative and support the idea that animal results can be used to predict human responses.

4. **Some test animals or organs of test animals are exquisitely sensitive to carcinogens, and such sensitivity invalidates use of results from such animals.**

Griesemer and Cueto (146) have analyzed the results of testing 190 chemicals in the NCI Bioassay Program (see discussion in *Expert Review of Bioassay Results* and app. A). They identified 35 chemicals that were "strongly carcinogenic" in either the rat or the mouse and noncarcinogenic in the other species. Of the 35, 18 were positive in the mouse and negative in the rat, and 17 were positive in the rat and negative in the mouse, which indicates that neither animal was much more often the sensitive species. However, 12 chemicals caused mouse liver tumors, no other lesion in the mouse and no lesions in rats. Taken by themselves these results suggest that the mouse liver is a sensitive organ.

Liver tumors are often found in mice but are infrequently found in U.S. citizens, although they occur frequently in human populations in other parts of the world. Should a chemical that causes mouse liver tumors be considered a hazard? An approach to resolving the mouse liver question was to review how predictive such results are for tumors in other animals. Tomatis, Partensky, and Montesano (343) showed posi-

tive correlation between a chemical's being oncogenic in the mouse liver and its being oncogenic either in the liver or at some other site in rats or hamsters. (Griesmer and Cueto (146) presented data only from rats and mice, and some mouse liver carcinogens in their compilation might be positive in animals other than rats.)

Despite the finding of Tomatis, Partensky, and Montesano (343) that mouse liver carcinogens were often positive at other sites or in other animals, IARC (185,187) considers mouse liver and lung tumors as "limited evidence" for carcinogenicity. However, OSHA (272) accepts mouse liver tumors as "indicators of carcinogenicity" if "scientific experience and judgment" are used in interpreting the data.

Crouch and Wilson (72) have analyzed some of the NCI Bioassay Program data. They calculated the potency and the standard error associated with potency of a chemical in causing a tumor at a particular site in either the rat or the mouse. In their analysis of 35 tested chemicals, they found that in 31 cases the potency in both rats and mice agreed within a factor of 10. Their analysis and similar analysis by Ames et al. (14), which consider the inherent error in experiments and the sensitivity of experiments, significantly reduces the number of chemicals that are positive in one species and negative in another. However, those analytical methods have not been generally applied to bioassay results.

5. Finding benign tumors in test animals has no value in defining carcinogenicity.

Tumors can be divided into two classes, benign and malignant. Benign tumors do not metastasize, the tumor cells remain in contact with each other and do not invade other tissues or organs. Malignant tumors can invade other tissues and metastasize, spreading to distant parts of the body and causing other tumors. Both types of tumors are found in experimental animals.

Hearings on pesticide regulations have been marked by repeated arguments about the importance of benign tumors. Should benign tumors found in experimental animals be taken as evidence that a chemical causes cancer?

The position that a benign tumor may later become malignant, that the line of demarcation between benign and malignant is unclear, and that benign tumors can also be life-threatening has prevailed in regulatory agencies. Therefore, no distinction is made in regulatory decisions between benign and malignant tumors. This is clearly reflected in FIFRA guidelines (102) and TSCA test standards (106) in which the endpoint is oncogenicity (tumor causation) rather than carcinogenicity (which emphasizes malignancy) (see table 27).

Griesemer and Cueto (146) reported no difficulty in deciding between benign and malignant tumors in the NCI Bioassay Program and that their conclusions about carcinogenicity were unaffected by including or excluding benign tumors. IARC statements reflect difficulties in the interpretation of benign tumors. As mentioned above, it considers the occurrence of some benign tumors as "limited evidence" for concluding that a chemical is a carcinogen (185). It also states that "preneoplastic lesions" may progress to "frank malignancy." Furthermore, IARC (186,187) considers that the occurrence of both preneoplastic and neoplastic lesions in the same organ strengthens conclusions about carcinogenicity.

Expert Review of Bioassay Results

In addition to the general objections to bioassay procedures that have been discussed, specific objections may be raised to particular tests. For instance, animals may have been inadvertently exposed to more than one chemical, to pathogenic micro-organisms, to extreme temperature, or to temporary deprivation of food or water, any one of which might influence results. Another frequent item of contention is whether or not a particular pathologic lesion indicates carcinogenicity. Critical reviews can reduce concern that flaws in experimental design or conduct mar the experiment or bring its results into question.

IARC periodically calls together panels of experts to review the worldwide literature about the carcinogenicity of particular chemicals or exposures. The IARC Monograph Program, be-

gun in 1970, had published reviews of bioassays of 422 chemicals and processes by 1979. For 60 of the 422 chemicals and processes, IARC was able to evaluate both human and animal evidence for carcinogenicity. Those 60 are described in the epidemiology section below.

For the remaining 362 chemicals and processes (185),

> . . . there was no information available from studies in humans [but] the IARC was asked repeatedly to consider making an assessment of the carcinogenic risk for humans which was based only on animal data.

In response to those requests, the IARC working group recommended (185):

> . . . that in the absence of adequate data in humans it is reasonable, for practical purposes, to regard chemicals for which there is *sufficient evidence* of carcinogenicity (i.e. a causal association) in animals *as if they presented a carcinogenic risk for humans* (emphasis in original).

An IARC working group defined five categories of evidence—sufficient, limited, inadequate, negative, and no data—against which experimental data are to be compared (see app. A). The working group decided that for 142 chemicals there was sufficient evidence, for about 100 there was limited evidence, and for the remainder there was inadequate evidence for carcinogenicity. The IARC exercise is especially important because it shows that experts from both the private and public sectors, sitting on IARC panels, can consider experiments and results and reach decisions about their meaning.

Griesemer and Cueto (146) analyzed the results of NCI's testing 190 chemicals. IARC (185) and Griesemer and Cueto (146) classifications of chemicals included 33 chemicals in common. Analysis of the classification of those 33 (see app. A) shows that there was good agreement about the more carcinogenic of the chemicals. Such agreement lends credence to the idea that tests carried out in different laboratories and analyzed by different experts can lead to similar conclusions about carcinogenicity.

Policy Considerations About Bioassays

General acceptance of bioassays as predictors of human risk is sometimes obscured by controversies about particular test results. The Federal Government, in response to controversies arising from testing artificial sweeteners or pesticides, has asked a number of expert panels to consider bioassay designs, results, and usefulness. In all cases, the panels endorsed bioassays while reserving judgment about particular tests and attaching caveats to some results. Table 28 is a listing of some Government-affiliated panels and reports plus two trade associations, the American Industrial Health Council (AIHC) and the Food Safety Council, and a union organization which have commented on bioassays.

The Office of Science and Technology Policy (OSTP), in the Executive Office of the President (281) produced a good, brief exposition of methods, a well-crafted list of recommendations about carcinogen testing, and suggestions for a Federal carcinogen policy. About bioassays, the report says,

> . . . it would seem prudent to view a positive test result in a carefully designed and well-conducted mammalian study as evidence of potential human carcinogenicity.

As indicated by the quote, some organizations urge consideration of experimental design and execution before drawing conclusions about carcinogenicity. AIHC (8), in commenting on OSHA's (278) proposed cancer policy, endorsed bioassays as predictors of human risk:

> There is agreement further that a substance which is a confirmed oncogen in two mammalian species should be subject to regulation as a probable human carcinogen.

All Federal regulatory agencies accept animal test results as predictors of carcinogenic risk for humans. The Interagency Regulatory Liaison Group (IRLG) was formed in 1977 to aline the policies of the Consumer Product Safety Commission (CPSC), FDA, the Food Safety and Quality Service of the Department of Agriculture, EPA, and OSHA. IRLG stated (180):

Table 28.—Some Organizations That Have Considered and Endorsed Animal Tests as Predictors of Human Risk From Chemical Carcinogens

Organization	Publication
The Secretary's (HEW) Committee on Pesticides and their Relationship to Environmental Health	Report (325)
National Research Council	— Evaluating the Safety of Food Chemicals (259) — Safety of Saccharin and Sodium Saccharin in the Human Diet (261) — Pest Control: An Assessment of Present and Alternative Technologies (262) — Principles for Evaluating Chemicals in the Environment (263) — Food Safety Policy (269)
Office of Technology Assessment	— Cancer Testing Technology and Saccharin (282) — Environmental Contaminants in Food (284)
National Cancer Advisory Board, Subcommittee on Environmental Carcinogenesis	— General Criteria for Assessing the Evidence for Carcinogenicity of Chemical Substances (245) — The Relation of Bioassay Data on Chemicals to the Assessment of the Risk of Carcinogens for Humans Under Conditions of Low Exposure (246)
American Industrial Health Council	— AIHC Recommended Alternative to OSHA's Generic Carcinogen Proposal (8)
Food Safety Council	— Proposed System for Food Safety Assessment (125)
Occupational Safety and Health Administration	— Identification, Classification and Regulation of Potential Occupational Carcinogens (279)
Interagency Regulatory Liaison Group	— Scientific Bases for Identification of Potential Carcinogens and Estimates of Risks (180)
Office of Science and Technology Policy	— Identification, Characterization and Control of Potential Human Carcinogens: A Framework for Federal Decision-making (281)
American Federation of Labor, Congress of Industrial Organizations, and United Steelworkers of America	— Post-Hearing Brief on OSHA's Proposed Standard on the Identification, Classification and Regulation of Toxic Substances Posing a Potential Occupational Carcinogenic Risk (7)

SOURCE: Office of Technology Assessment

> Evidence of the carcinogenic activity of an agent can be obtained from bioassays in experimental animals.

and,

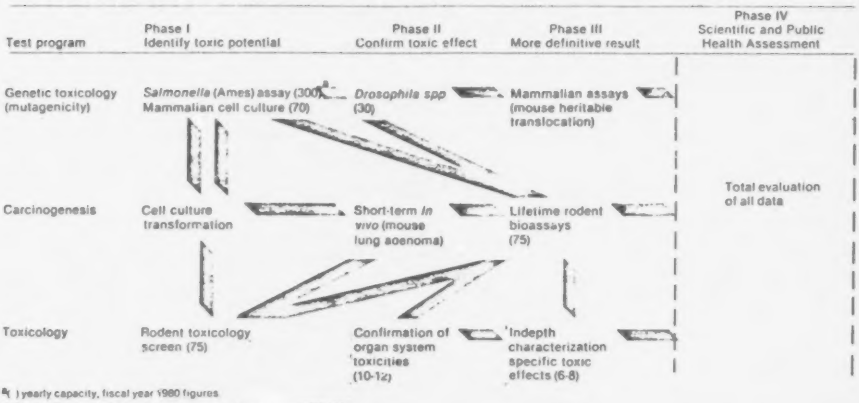
> Positive results, obtained in one species only are considered evidence of carcinogenicity. Positive results in more limited tests (e.g., when the observation period is considerably less than the animal's lifetime), but by experimentally adequate procedures, are acceptable as evidence of carcinogenicity. Negative results, on the other hand, are not considered as evidence of lack of a carcinogenic effect, for operational purposes, unless minimum requirements have been met.

As these quotes show, both AIHC and IRLG accept bioassays as predictors of potential human risk. However, they differ in the weight of evidence each requires. AIHC wants positive test results in two species before making decisions about carcinogenicity, while IRLG will consider making a decision on the basis of positive results in one species. Labor organizations (e.g., American Federation of Labor, Congress of Industrial Organizations, and United Steelworkers of America (7)) and environmental groups also consider positive results in a single animal as sufficient to make a judgment about carcinogenicity.

How Many Chemicals Are Carcinogens in Animal Tests?

The number of chemicals that are carcinogenic in humans or animals is uncertain. A few estimates have been made, but the bases for the estimates are poor.

Figure 20.—Interrelationships of Major Testing Activities of NTP



[a]) yearly capacity, fiscal year 1980 figures.
SOURCE: Office of Technology Assessment, adapted from NTP (272)

sence of arrowheads on the lines is intentional; according to David Rall, NTP Director (303), there has not yet been enough experience with the scheme to be certain which phase I tests should come first or whether all chemicals should go through all phase I tests.

A critical feature of tier testing is the ability to make decisions about whether or not to continue testing from phase I to II, or from II to III. Guidelines are necessary for making the decision that a chemical is sufficiently without risk and that no further testing is necessary. Rall (303) said that development of decisionmaking guidelines is a priority item for NTP in 1980 and 1981. NTP intends to analyze the testing histories of chemicals that have gone through all three phases (albeit not necessarily under NTP aegis) to determine which test results were most predictive of the ultimate decision about the chemical. NTP will take advantage of the fact that the most expensive and time consuming testing, phase III, has been completed on some chemicals which have not otherwise been tested. Such chemicals will be entered into phase I and II testing to provide additional information about which tests are most predictive. Finally, the NTP decision to continue testing a few chemicals that are negative in phase I tests will provide additional information.

EPIDEMIOLOGY

Lilienfeld (210) defined epidemiology as the study of the distribution of disease in human populations and of the factors that influence disease distribution. Epidemiologic techniques are useful for identifying causative agents and conditions that predispose for cancer. Studies can determine associations in populations between exposure to carcinogenic agents or between aspects of lifestyle and increased cancer risk.

The earliest association of a factor with cancer was made by Ramazzini in 1713. He found that nuns had a higher rate of breast cancer than other women and, in his Treatie on

the Diseases of Tradesman of 1700, he attributed the increase to celibacy (322). That association has been sharpened to include the observation that women who deliver a child at an early age are less likely to develop breast cancer. In addition to identifying cancer risks, epidemiology may play a positive role by pointing out less hazardous diets or agents which are protective against cancer.

For the purpose of this discussion, epidemiologic studies are divided into three general types: 1) experimental, 2) descriptive, and 3) observational. While several basic strategies exist, there are no rigid study designs within any of these categories. Flexibility is important since, unlike laboratory experiments, epidemiology examines groups of unpredictable people living in dynamic environments. The importance of flexibility is underlined by IRLG Guidelines, which state that epidemiologic study design must "be described and justified in relation to the stated objective of the study" (181).

Experimental Epidemiology

The ideal procedure for investigating cause-and-effect hypotheses is through experimental epidemiology. This type of study requires the deliberate application or withholding of a factor and observing the appearance or lack of appearance of any effect. Given the severity of cancer, ethical considerations preclude the administration of suspected carcinogens to people, though it is possible to test agents thought to aid in prevention (292).

Experimental epidemiology studies are difficult to conduct because of the need to secure the cooperation of a large group of people willing to permit an experimenter to intervene in their lives. The investigator must have reason to believe that the proposed intervention, whether a deliberate application or withholding, will be beneficial, but at the same time, he must be somewhat skeptical of the effects. Once sufficient evidence leads to the conclusion that the intervention is or is not beneficial, the experiment must be terminated.

Descriptive Epidemiology

Descriptive epidemiology studies examine the distribution and extent of disease in populations according to basic characteristics—e.g., age, sex, race, etc. The primary purpose of conducting descriptive epidemiologic studies is to provide clues to the etiology of a disease which may then be investigated more thoroughly through more detailed studies. Descriptive studies have focused on international comparisons and comparisons among smaller geographical regions, such as U.S. counties (29).

The identification of high bladder cancer rates in New Jersey males and excess mortality rates from cancer of the mouth and throat, esophagus, colon, rectum, larynx, and bladder in the industrialized Northeast have suggested that occupational factors might be incriminated and have prompted additional investigations. Blot et al. (29) describe NCI's stepwise approach to search for etiological clues. Examination of age-specific rates of disease occurrence or mortality across time (see ch. 2) is another example of descriptive epidemiology.

Observational Epidemiology

Observational epidemiology depends on data derived from observations of individuals or relatively small groups of people. These studies are analyzed using generally accepted statistical methods to determine if an association exists between a factor and a disease and, if so, the strength of the association. Often the hypothesis to be investigated arises from the results of a descriptive study. NCI has embarked on several observational studies based on findings from their county-correlation studies. For example, high rates of lung cancer were found in the Tidewater Virginia area, and a large study was initiated which found elevated risk for lung cancer in shipbuilders and smokers.

Cohort Studies

Two types of observational epidemiology studies, cohort and case-control studies, differ

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in the selection of the population groups for study.

A cohort study starts with a group of people, a cohort, considered free of the disease under study, and whose disposition regarding the risk factor under consideration is known. Usually the risk factor is an exposure to a suspect carcinogen or a personal attribute or behavior. The group is then studied over time and the health status of the individual members observed. This type of study is sometimes referred to as "prospective" because it looks forward from exposure to development of the disease characteristic (210,225). Cohort studies can be either concurrent or nonconcurrent in design. Concurrent cohort studies depend on events which will occur in the future, while nonconcurrent cohort studies rely on past data or past events.

Case-Control Studies

In a case-control study, individuals with the disease under study (cases) are compared to individuals without the disease (controls) with respect to risk factors which are judged relevant. Some authors label this study design "retrospective" because the presence or absence of the predisposing risk factor is determined for a time in the past (210,225). However, in some cases the presence or absence of the factor and the disease are ascertained simultaneously.

The choice of appropriate controls is rarely without problems. Often, for practical reasons, controls are chosen from hospital records. However, they may not be representative of the population, and they therefore may introduce "selection bias," as discussed by MacMahon and Pugh (218).

In case-control and cohort studies, the groups selected should be comparable in all characteristics except the factor under investigation. In case-control studies, the groups should resemble each other except for the *presence* of the disease, while in cohort studies, the study and comparison groups should be similar except for *exposure* to the suspect factor. Since this rarely is possible in practice, comparability between groups can be improved by either matching individual cases and controls (in case-control studies) or by standard statistical adjustment procedures (in either case-control or cohort studies). Demographic variables, e.g., age, sex, race, socioeconomic status, are most commonly used for adjustment or matching.

There are advantages and disadvantages with both the case-control and cohort studies (see table 29). Case-control studies tend to be less expensive to conduct, require relatively fewer individuals, and many have been especially useful in studying cancer. The great advantage of cohort studies is that they allow observation of all outcomes, not only those originally anticipated. Bias is somewhat reduced in cohort studies since classification into an exposure category cannot be influenced by prior knowledge that the disease exists. In a concurrent cohort study, it is often necessary to wait many years for the manifestation of enough disease cases to conduct an analysis. The cost and time of the study can be reduced if conducted nonconcurrently. Cohort studies tend to require many more subjects than case-control studies and assignment of individuals to the correct cohort for analysis is difficult.

Causal Associations

A pragmatic view of causality is necessary, particularly when studying complex, multifactorial diseases such as cancer. Analysis of the association between exposure and disease in an epidemiologic study depends on tests of statistical significance. However, finding a positive statistically significant association is not sufficient to conclude a causal relationship. Artifactual and indirect associations must be considered. As MacMahon and Pugh (218) state, " . . . only a minority of statistical associations are causal within the sense of the definition, which requires that change in one party to the association alters the other."

Policy Considerations About Epidemiology

While short-term tests and bioassays are used to evaluate a chemical's carcinogenic potential in the laboratory, the effect on humans is direct-

Table 29.—Advantages and Disadvantages of Case-Control and Cohort Studies

Type of study	Advantages	Disadvantages
Case-control	Relatively inexpensive	Complete information about past exposures often unavailable
	Smaller number of subjects	Biassed recall
	Relatively quick results	Problems of selecting control group and matching variables
	Suitable for rare diseases	Yields only relative risk
Cohort	Lack of bias in ascertainment of risk factor status	Possible bias in ascertainment of disease
	Yields incidence rates as well as relative risk	Large numbers of subjects required
	Can yield associations with other diseases as by-product	Long follow-up period
		Problem of attrition
		Changes over time in criteria and methods
		Very costly
		Difficulties in assigning people to correct cohort

SOURCE: Office of Technology Assessment.

ly assessed by epidemiologic techniques. Well-conducted and properly evaluated epidemiology studies which show a positive association are accepted as the most convincing evidence about human risks.

Negative epidemiologic results show that exposure of a certain number of people to a substance at a specified level did not cause cancer. From such results, it is possible to calculate that human risk is no higher than what the study could have detected. For instance, a study of 1,000 people which showed no excess cancer would be "more negative" than one of 100 people exposed at the same level. Neither study would show that a risk exists, and neither shows that no risk exists, but the larger study shows a lower probability of risk.

The OSHA Generic Cancer Policy (279) proposed that OSHA, after ascertaining the adequacy of the study design, would interpret negative epidemiologic studies as setting an upper limit for human risk. AIHC (8) wants negative human evidence to be considered along with animal data in making decisions about carcinogenicity. The OSHA position, and that of Federal Government regulatory agencies in general (306), is to use epidemiology to estimate limits of risk, but not to weigh negative human evidence against other positive evidence in deciding whether or not a substance is a carcinogen.

The Regulatory Council (306) considers properly designed and conducted epidemiologic studies, which show a significant statistical relationship between human exposure to a substance and increased cancer risk, to provide "good evidence" that a substance is carcinogenic. The Council mentioned some difficulties in epidemiology, e.g., long latency periods, multiplicity of exposures, and cautioned that often "even large increases (which could involve thousands of people) . . . cannot be detected." For these reasons they cite two caveats in using epidemiological studies:

> The failure of an epidemiological study to detect an association between the occurrence of cancer and exposure to a specific substance should not be taken to indicate necessarily that the substance is not carcinogenic.
>
> Because it is unacceptable to allow exposure to potential carcinogens to continue until human cancer actually occurs, regulatory agencies should not wait for epidemiological evidence before taking action to limit human exposure to chemicals considered to be carcinogenic.

OSTP (281) states that "a positive finding in a well-conducted epidemiologic study can be viewed as strong evidence that a chemical poses

a carcinogenic risk to humans." Alternatively, "a negative finding is not nearly so meaningful . . . " and OSTP emphasizes the importance of examining the sensitivity of a negative study, and suggests that the upper limit of risk that might have gone undetected in the study be calculated and presented.

Carcinogens for Which There Is Human Evidence

Through various means, epidemiologic studies have identified several human carcinogens. The first use of epidemiologic principles to relate environmental contaminants to human cancer is credited to Pott in 1775 (322). Pott, a physician in London, suggested that scrotal cancers, which he observed in men who had worked as chimney sweeps when boys, were caused by exposure to soot. Pott is an example of an astute physician recognizing an unusual cluster of cancer cases. A more recent example is vinyl chloride which was identified as a carcinogen after three cases of a rare liver tumor (hepatic angiosarcoma) were diagnosed in workers in a manufacturing plant (71). In the case of vinyl chloride, evidence for its carcinogenicity in laboratory animals was available in advance of the human evidence. In both cases, control action followed the demonstration of occupational risk. The Danish Chimney Sweeps Guild instructed its members about protective clothing and to practice preventive hygiene soon after Pott's report was published, and OSHA regulated vinyl chloride.

IARC bases its evaluation of carcinogenic risk to humans on consideration of both epidemiological and experimental animal evidence. IARC considered human evidence bearing on 60 chemicals and industrial processes and classified 18 as human carcinogens (see table 30). Many of the human data considered by IARC are from studies concerning workplace and medical exposure. This does not necessarily reflect the distribution of carcinogens but more likely the higher exposure and relative ease of performing epidemiologic studies on patients and occupational groups. For instance, the availability of medical records facilitates locating people exposed to a drug and provides information about time of exposure and dose level.

IARC also classified 18 additional compounds as *probably* carcinogenic for humans but there was insufficient evidence to establish causal associations. These 18 were further subdivided according to the degree of evidence, high or low, as displayed in table 30. Insufficient evidence was available to decide about the carcinogenicity of 18 chemicals listed in table 30. Finally, because of time limitations, IARC was unable to evaluate six compounds for which human data exist.

Annual Report on Carcinogens

In an effort to provide information on carcinogens which would be useful to regulatory agencies, Congress passed an amendment to the Community Mental Health Act (Public Law 95-622). It requires the Secretary of DHHS to publish an annual report containing a list of substances which are known to be carcinogens or may reasonably be anticipated to be carcinogens and to which a significant number of persons residing in the United States are exposed. The task was assigned to NTP, and the first report (82) includes the 26 exposures which IARC had determined in 1978 to be human carcinogens (344). Candidates for the 1981 and 1982 list also will be drawn from IARC beginning with chemicals and processes judged "probably carcinogenic for humans." The initial report did not, as required by the statute, list " . . . all substances which either are known . . . or . . . may reasonably be anticipated to be carcinogens . . . . "

One limitation enumerated in the first report was that, "Science and society have not arrived at a final consensus on the definition of carcinogen either in human populations or in experimental animals." The report, by including chemicals and industrial processes already classified by IARC, has sidestepped dealing with the question of what is a carcinogen. A definition for "carcinogen" remains elusive unless it is given in the context of a particular methodology.

5. Extrapolation From Study-Generated Data to Estimates of Human Risk

INTRODUCTION

Information about carcinogenicity is obtained from exposing animals to measured doses of suspect substances in the laboratory or by studying associations between exposures to suspect carcinogens and development of cancer in humans. In practice, both the animals and certain groups of humans, particularly those exposed in the workplace, are exposed to doses far larger than those encountered by most citizens. A number of "numeric extrapolation" methods have been developed to estimate the effect of exposure to low doses based on observed effects at high doses. When information about carcinogenicity is obtained from animals, "biologic extrapolation" techniques are employed to project from animal results to estimates of human risk. (In this report the word "hazard" is applied to a substance or exposure that harbors a "risk" to people who come in contact with it—i.e., a carcinogenic chemical is itself a hazard. Risk is the probability of cancer developing as a result of a particular exposure to the hazard.)

In most cases, no adequate human data are available for estimating risks, and it is necessary to make both numeric and biologic extrapolation from measured responses in animals to estimate human risk. Less uncertainty attends making numeric extrapolations from observation of human responses at high exposure levels than extrapolations from animal data. However, such extrapolations are often complicated by poor exposure data.

Extrapolation, like testing, is employed to make regulatory decisions, and as in the case of testing, a number of agencies have made statements about the methods they will employ. These policy statements are necessary to explain, in the absence of agreed-on universal procedures, how the agencies intend to use bioassay and epidemiologic data to estimate risk through the use of extrapolation methods.

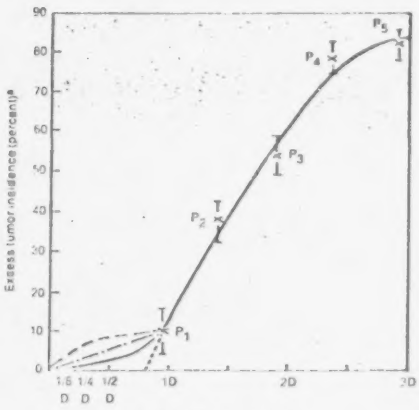
NUMERIC EXTRAPOLATION

This discussion describes information that can be obtained from extrapolation, and comments on various extrapolation methods. It is neither rigorous nor inclusive, and the interested (and mathematically sophisticated) reader is referred to Hoel et al. (170), Crump et al. (75) and the Food Safety Council (FSC) (125) for such treatments.

Toxicity testing produces data relating tumor incidence (I) to dosage (D) as shown in figure 21. Generally, a smooth curve drawn between the experimental points, P_1-P_5, (solid line in figure 21) is sigmoidal, or S-shaped. It can be seen that the incidence of tumor formation decreases with decreasing dosage. The crux of the extrapolation problem is what sort of line best approximates the response in the region for which data are not available. Or, what kind of line should be drawn from point P_1 to lower, unmeasured, response levels.

Graphic representations such as figure 21 do not fully show the difficulties in estimating in-

Figure 21.—A Stylized Dose-Response Curve and Some Extrapolated Curves



*Excess tumor incidence (percent) is defined as:

$$\frac{\text{tumors in exposed population}}{\text{number of exposed population}} - \frac{\text{tumors in control population}}{\text{number of control population}} \times 100$$

— — linear extrapolation
— · — · — supralinear extrapolation
— · · — · · — line proposed as a threshold

SOURCE: Office of Technology Assessment.

cidence at very low doses. The first division on the vertical incidence scale is 10 percent, which means that 1 human or animal out of 10 developed cancer. For many agents, especially those present in air or water, we are interested in knowing what dose is projected to cause an incidence orders of magnitude less, e.g., 1 tumor in 100,000 animals or humans. Such small fractions cannot be seen on the figure, but they can be calculated using any extrapolation method.

The solid curved line drawn from point P_1 to the origin is a continuation of the curve constructed between the experimentally determined points. It was drawn by eye, and it is representative of a number of smooth, concave upward lines that can connect P_1 and the origin as a continuation of the sigmoidal curve constructed between P_1 and P_5.

The Question of Thresholds

The solid line on figure 21 embodies the premise that there is no threshold. A threshold model would have the curve hit zero incidence at some dose greater than zero, as is shown in figure 21.

The threshold argument contends that there are doses of carcinogens so low that they will not cause cancer, and that no matter how many animals are exposed to doses that low or lower, no tumors will result. The counterargument is that any dose of a carcinogen, no matter how small, has a finite although small, chance of causing a tumor, and, if an experiment were performed with a sufficiently large number of animals, such risk would be detectable.

The concept of a population threshold, which is discussed here, includes the idea that there are exposure levels below which no individual in the population will develop cancer. No solution to the threshold/no threshold argument can be found by doing increasingly larger experiments with more and more animals. If a given dose of chemical causes no excess tumors in 1,000 animals, there is no guarantee that it will not cause an excess when 2,000 are exposed.

Individuals may have thresholds, as suggested by the fact that all heavy cigarette smokers do not develop lung cancer. Possible biologic reasons advanced to explain such differences in susceptibilities include physiologic and genetic variations among people. Another reason for the apparent differences in susceptibility may be chance. Some heavy smokers may be "luckier" than others in that their exposures do not trigger carcinogenesis, and they may not develop cancer, or they may die from some other cause before cancer develops. In any case, it is as yet impossible to predict an individual's threshold for even a single carcinogenic agent and impossible to derive a population's threshold with current knowledge or methods.

In a highly recommended article, Maugh (224) reports on conversations with a number of scientists and administrators from the National

Institutes of Health, private testing laboratories, and industry. The conclusion of the article, apparently shared by the interviewed scientists and administrators, is that resolution of the threshold question is not now available:

> . . . it is extremely unlikely that it would be possible to distinguish between a linear dose-response curve and a highly nonlinear one (threshold), even in a large-scale experiment involving several thousand animals per dose level.
>
> . . . statistical analysis of standard animal carcinogenicity experiments, Schneiderman [then-Associate Director of the National Cancer Institute (NCI)] concludes, does not now, and probably never will, resolve the threshold question. There are, he says, simply too many "biologically reasonable" mathematical models, both implying and denying the existence of thresholds, that will fit the observed results.
>
> . . . there is so little data and so many interpretations, Gehring [Dow Chemical Co.] says, arguing about thresholds is an exercise in futility.

The view that thresholds cannot be demonstrated is accepted in publications of the National Research Council (NRC) (262), Interagency Regulatory Liaison Group (IRLG) (180), FSC (125), and, for tumors resulting from somatic mutations, by the American Industrial Health Council (AIHC) (8). Despite the apparent agreement that it is impossible to demonstrate a threshold, many individuals object to the idea that thresholds should not be considered in making decisions about carcinogens.

In particular, some tumors are thought to result from irritation or mechanical injury, and threshold models are postulated for those. An often mentioned example is Clayson's (60) finding that bladder stones are found in conjunction with some bladder tumors. Stone formation may be dependent on intake of large quantities of a chemical; if exposure to the chemical is sufficiently low so that no stones are formed and if stone formation is necessary for carcinogenicity, then a threshold should exist. This and other examples of "epigenetic" tumors can be considered separately from tumors that originate from somatic mutations. Just as thresholds for acute toxic responses differ, thresholds for stone formation most likely differ among individual animals. Therefore, it may be impossible to determine exactly what dose is necessary to produce a stone and therefore pave the way to a tumor. Nevertheless, if the threshold for stone formation in animals is found to be 100 or 1,000 times greater than human exposure levels, the observation takes on great significance. If stone formation is a necessary precursor to tumor appearance, and no stone formation occurs at human exposure levels, it becomes difficult to maintain the position that human exposure levels present a carcinogenic risk. The difficulties in this argument are the possibility that some humans may produce stones at very much lower doses than animals and that carcinogenicity might not proceed through stone formation in humans. Such caveats seem reasonable to some people; unreasonable to others. Experimentation and more sophisticated models may eventually settle such questions. However, for the present, positions on these issues reflect organizational policy and individual judgment.

Gehring, Watanabe, and Young (139) describe differences between metabolism of chemicals administered at low and high doses. Measurement of these differences is called pharmacokinetics. In general, biochemical mechanisms to detoxify chemicals and to repair damage to DNA are seen as having a better chance of detoxifying and repairing damage at low doses than at high doses. High doses can swamp defense mechanisms resulting in toxic effects; lower doses are seen as presenting little or no risk.

Metabolic differences measured by pharmacokinetics might have important effects on the shape of the dose-response curve. If a metabolite of an ingested substance is the actual carcinogen, and the production of the metabolite increases out of proportion to dose above a certain level, then the dose-response curve might bend upward at that point. Pharmacokinetic data are not always collected, and the standard bioassay which produces data at only two dose levels does not provide sufficient information to see if differences in metabolism might be important in the slope of the dose-response curve.

Biochemistry of a particular compound may be affected by other compounds present in the organism. Cancer is a relatively common disease, and if avoiding cancer involves biochemical detoxification processes, it may be that small doses of many substances can swamp the process as well as large doses of a single substance. If this is correct, the addition of the carcinogens, even at low doses, might be enough to overcome the detoxification mechanism.

Cornfield (67) described quantitative extrapolation models to take into account differences in metabolism at high and low doses. His paper was criticized because it postulated a threshold (see 36,73,229,276,319), and his hope that the paper would lead to discussion of the merit of his models apparently was not realized (68). The difficulty with models which propose detoxification activities for producing thresholds is that the detoxification has to be instantaneous and complete. Otherwise molecules might escape detoxification and initiate a carcinogenic event.

Donald Kennedy, a few months after leaving the post of Commissioner of the Food and Drug Administration (FDA), expressed his opinion that thresholds may exist for some chemicals:

> Dr. Kennedy said that the [Delaney] clause in the FDA's authorizing legislation codifies the hypothesis that there is no threshold concentration below which a chemical does not cause cancer. And although this hypothesis "probably holds most of the time," Dr. Kennedy said that he was "as certain as I can be of any scientific prediction that some day, very soon, some compound will be demonstrated to have a threshold level for cancer causation" . . . (274).

It is difficult, if not impossible, to marshal more evidence on one side of the threshold question than on the other. The ascendancy of the more conservative view, that thresholds cannot be identified for human populations, can be taken as a policy decision made in the interest of protecting the public health. Such a general policy can not exclude the possibility that a threshold may someday be demonstrated.

Numeric Extrapolation To Project Risk at Doses Below Those Tested

The shape of the line in figure 21 depends on the number of tumors observed at points P_1-P_3. No matter what method is used to extend the line below P_1, that extension represents an estimate. Any number of smooth curves can be drawn from point P_1 to the origin; for convenience, the possible lines will be divided into three families: supralinear, linear, and infralinear. A detailed discussion of these models as they relate to radiation and cancer is available in a paper by Sinclair (329).

Supralinear Extrapolation

A supralinear extrapolation is presented on figure 21. It says that some doses less than 1D are relatively more effective in inducing tumors than doses equal to 1D. Conceptually the contention that lower doses are more carcinogenic is easy to address. Further tests at lower doses would resolve the question, but additional tests are costly and time consuming.

Supralinear models are considered for two reasons. In several NCI bioassays, the tumor yield was lower at the high dose than at the low dose (102). In other words, the lower dose was more efficient at producing tumors. The explanation is that the higher dose was so toxic that it killed animals before they developed tumors. The other reason for considering supralinear responses is that some studies of radiation-induced cancer have been interpreted as producing supralinear dose-response curves (e.g., 241), but those interpretations are hotly disputed.

Such responses might result from the presence of a subpopulation of more sensitive individuals. On figure 21, the supralinear response between the origin and P_1 represents the tumors induced in the proposed sensitive fraction of the population; the solid line drawn from the origin to P_3 represents the sensitivity of the remaining members of the population. The difference between the two lines between the origin and P_1

represents the contribution of the sensitive subpopulation to the total response at doses below 1D. It can be seen that the sensitive subpopulation accounts for the majority of tumors that occur below P_1. Clearly, if this model describes risks, reducing doses to ½D or ¼D would not significantly reduce tumor incidence, and a supralinear dose-response curve would force lowering doses to very small fractions of D to significantly reduce tumor incidence.

Nonartifactual, supralinear dose responses have rarely been observed in bioassays but neither would they be expected. Laboratory animals are highly inbred and each animal should be more nearly equally sensitive than are members of human populations. Supralinear response models have been advanced but do not now receive the acceptance accorded to the other two general models.

Linear Extrapolation

A linear model is shown by the straight line that extends from P_1 to the origin on figure 21. If the true dose-response curve is represented by the solid curved line from P_1 to the origin, then the linear model is "conservative" and overestimates the number of tumors at all doses between P_1 and the origin.

The paper by Crump et al. (75) is an often-cited and important argument for linear dose responses at low doses. The paper points out that 25 percent of the U.S. population will develop cancer as a result of existing carcinogenic influences (see ch.3). Crump et al. (75) propose that any new carcinogenic substance interacts additively with exposures and behaviors already present in the environment. Their mathematical theories predict that regardless of the shape of the dose-response curve at high exposures, at low doses cancer incidence should be proportional (linear) with exposure to the substance under study.

Gaylor and Kodell (137) argue that no risk estimate can be very reliable for doses below that associated with the lowest data point (P_1 in figure 21) because there is no information available below point P_1. They propose the use of "linear interpolation" and the 95-percent upper confidence level to estimate the *maximum* risk posed by a substance.

Error is associated with any experimental determination, and standard methods can be used to calculate "confidence limits" for each estimate. Usually "95-percent confidence limits" are calculated for carcinogenicity experiments; they are plotted as vertical bars extending from the data points, as shown on the figure. The 95-percent confidence limit says that given the experimentally determined incidence and the size of the experiment, we can be 95 percent certain that the actual incidence represented by the point estimate lies inside the error limits.

In the method of Gaylor and Kodell (137) a line is drawn from the upper limit of the error bar on the lowest data point to the origin. Inspection of figure 21 shows that this method projects a larger risk than does linear interpolation from the point P_1 to the origin. This is not an estimate of risk; it is an estimate of the upper bound of risk.

Objections to including upper confidence levels in extrapolation are frequently voiced. The practice of including them is seen as introducing a "safety factor." Industry spokesmen (9a) and others contend that the best risk estimate should be made and the safety factors added after the estimate is made.

As a practical matter, there is often no alternative to the linear model. The dose-response curve in figure 21 is an outrageous overstatement of the data that are generally available. Bioassays carried out according to NCI's cancer testing guidelines (331) produce only two data points. The Environmental Protection Agency's (EPA) (102) analysis of many such tests showed that tumor incidence was sometimes higher and sometimes only measurable at the lower of the two doses because other toxic effects killed animals at the higher dose. Left with only the response at the lower dose, there is little choice available but to estimate responses at still lower doses on the basis of simple proportionality. Such calculations produce a straight line from the experimental point to the origin.

IRLG (180) did not discuss how to extrapolate when more than one data point is available; it

recommends linear extrapolation (proportionality) for making estimates from a single point. IRLG further proposes that the upper confidence level be used as the starting point for extrapolation to achieve "an added degree of protection . . . ."

A linear extrapolation model from the lowest positive data point to zero dose (104) was used by EPA's Carcinogen Assessment Group (CAG) until the summer of 1980. At that time, CAG (48) announced it was going to discontinue use of the linear model and subsequently employ a model developed by Crump. The CAG decision was not made because evidence had shown the linear model was poorer than the new one (48):

> There is no really solid scientific basis for any mathematical extrapolation model which relates carcinogen exposure to cancer risks at the extremely low level of concentration that must be dealt with in evaluating the environmental hazards.

The now-adopted model is linear at low doses, and, in practice, produces estimates of risk at low doses which " . . . are not markedly different from those obtained with the former procedure based on the one-hit [linear] model" (230). However, the new model does allow consideration of data produced above the linear part of the curve (points P_4 and P_5 on figure 21) to influence the slope of the line and the range of error associated with each point.

Infralinear Extrapolation

The curved line between P_1 and the origin on figure 21 or any curved line which remains below the straight line is infralinear. Such models predict lower tumor incidence than the linear model. If it were decided that a certain level of risk were acceptable, higher exposure to the chemical would be allowable under infralinear than under linear models.

A number of such models have been developed and are well described in FSC's (125) report. All of them produce concave upward lines between the origin and the lowest data point (P_1, in figure 21). Different models produce differently shaped lines. It is suggested (e.g., 125) that the model which produces the line that best fits the data points (P_1 to P_5 in figure 21) is the model to use to predict risk between P_1 and the origin. Unfortunately, usually any of the models seems to fit the available data points about equally well (9a,125,138,180). The reasons for the equally good fits are that generally only one, two, or three data points are available and all of them measure incidence above 10 percent. Data points at such relatively high response rates do not often provide enough information to decide what the dose-response curve is at an incidence of 1 percent or less.

QUANTITATIVE EFFECTS OF SELECTING A MODEL

Selection of the appropriate model for estimating risks at low doses would be made easier if some models clearly did not fit the observed data points. As mentioned above, hardly ever is it possible to select the best model or even to reject the worst on the basis of fit to observed data points. The low end of the dose-response curve is most informative for selecting the correct model but it is the part that is most difficult to measure. In practice, incidence rates in animal tests much below 10 percent (5 tumor-bearing animals in a test population of 50) can seldom be distinguished from the rate of spontaneous tumors.

Table 32, derived from a paper by Brown (35), shows that two infralinear models and the one-hit model, which is essentially linear at doses that cause an incidence of 10 percent or less, are indistinguishable at high doses. For the table, a dose level of one was set as sufficient to cause an incidence of 50 percent. The expected incidence using higher doses or doses as low as one sixteenth are nearly equal regardless of the

Table 32.--Expected Incidence of Tumors Calculated by Three Models When a Dose of 1.0 Caused Tumors in 50 Percent of the Tested Animals

	Projected percentage of tumor bearing animals		
Dose level	Log-normal model (Infralinear)	Log-logistic model (Infralinear)	Single-hit model (linear at incidence below 10%)
16	98	96	100
4	84	84	94
1	50	50	50
1/4	16	18	16
1/16	2	4	4
1/100	0.05	0.4	0.7
1/1,000	0.00035	0.026	0.07
1/10,000	0.0000001	0.0018	0.007

SOURCE: Adapted from Brown (35)

model. Brown (35) points out that no experiment of practical size could distinguish among the three models at those dose levels.

However, at much lower dose levels of 1/100, 1/1,000, and 1/10,000, the models diverge greatly in their projections of incidence. These greatly lower dose and response levels are often the ones of most interest for estimating human risks, but they cannot be measured. The incidences measured at higher doses do not provide sufficient information to choose the appropriate model. These problems plague all extrapolation efforts.

In general, either a linear or infralinear model is used for extrapolation. The linear model predicts a higher incidence at low doses than does the infralinear model.

Selection of the correct extrapolation model is important for only one of the three possible regulatory strategies for carcinogens. The first strategy is to accept either human or animal evidence as sufficient to identify carcinogens, and once the identification is made, try to eliminate the exposure. This approach requires no quantitative or numeric extrapolation. The second approach uses biologic and numeric extrapolation to rank substances in order from that expected to be most carcinogenic to those that are noncarcinogenic. This relative ranking can be accomplished by consistently applying any model, and the numerical accuracy of the estimated incidence is not critical. The third approach, which includes a quantitative estimate of human risk to be used in risk-benefit computations or to consider levels of acceptable risk requires the most accurate numerical estimate. Clearly, in this case, the selection of models is important because the numbers produced by different models vary across a wide range.

Virtually Safe Doses

A very low risk of cancer, say, one chance in million lifetimes, is sometimes suggested as a virtually safe dose. Any extrapolation model can be used to calculate the dose which will produce such a risk, and different models produce very different estimates for the virtually safe dose (see table 32 and 125,170). As shown on figure 21, infralinear models predict higher virtually safe doses (i.e., lower risks at any dose) than does the linear model.

WHAT QUANTITATIVE PROJECTIONS CAN BE MADE FROM NEGATIVE RESULTS (ZERO EXCESS TUMORS IN A TEST POPULATION)?

No tumors occurring in a test population of 100 animals or no excess tumors among 100 animals as compared with the number of tumors in 100 control animals does not show that zero cancer risk is associated with the chemical. Instead standard statistical calculations based on zero excess tumors in 100 animals show that we can be 95-percent confident that the actual incidence of tumors is no more than 4.5 percent. This estimate of the incidence of tumors that might have gone undetected is called the upper confidence limit. The percentage can be reduced by testing more animals, for instance, finding zero excess tumors in 1,000 animals would mean that we can be 95-percent confident that the actual incidence is no more than 0.45 percent.

Proceeding with the illustration of zero excess tumors in 100 animals, assume that the dose administered to the animals was 1,000 times higher than that to which humans are exposed. Linear extrapolation (proportionality) predicts that exposure of the U.S. population to that chemical at 1/1,000 the level fed to the animals will result in fewer than 10,000 cases of cancer assuming equal sensitivity between man and animals. The estimated risk would be reduced if the experiment on which it is based is more sensitive. For instance, finding zero excess tumors in 1,000 animals (instead of 100) would reduce the estimated risk to fewer than 1,000 cases.

The statistics of the above exercise are not questioned, but they are seldom applied. Although a test cannot show that a substance presents no risk, much less concern is attached to substances that cause no excess of tumors. The risk associated with substances that are negative in bioassays is qualitatively lower, and the consideration of quantitative risk estimates from negative experiments is of minor importance.

OTHER EXTRAPOLATION MODELS

The supralinear, linear, and infralinear models are all dichotomous. They compare the number of tumors or tumor-bearing animals in the exposed population to the number in the controls. In both populations, the analysis depends on the presence or absence of tumors. Other models can be used to make inferences about the times (or ages) at which animals develop tumors in response to exposures.

Two of these models have been used extensively to describe animal and human "time-to-tumor" data. The lognormal model described in Chand and Hoel (57), predicts that the average time-to-tumor is longer at low doses. An important outcome of this model is that at sufficiently low doses, the time necessary for tumor development may exceed the expected lifespan. Such a long latent period would produce a "practical threshold." The Weibull model (also described in 57) predicts that the average time-to-tumor is nearly independent of dose. This prediction means that an increase in dose simply causes more cancers; it does not shift the age distribution at which they occur. The assumptions and predictions of these two models are quite different. Unfortunately both are apt to give adequate fits to any available data set, making it difficult to reject one in favor of the other. IRLG (181) concluded that these models have not received the attention that has been focused on dichotomous dose- incidence relation models, and it recommends more research be directed toward exploring them. The mathematics for these models is sophisticated, and the interested reader is referred to Chand and Hoel (57).

At this time, discussion of other models is more an academic than a policy exercise. Opposing camps are for or against quantitative ex-

trapolation, and among those favoring it, the argument is between those for and against using linear extrapolation (including EPA's new model). There is no agreement about another single model being offered as an alternative at this time.

EXTRAPOLATION FROM SHORT-TERM TESTS TO HUMAN RISKS

McCann et al. (227) and McCann and Ames (226) showed that about 90 percent of the carcinogens tested in the Ames test were mutagenic (see ch. 4). Meselson and Russell (235) developed a model to compare the mutagenic and carcinogenic potency of tested chemicals. Fourteen chemicals were analyzed because there were sufficient mutagenic and carcinogenic data available to construct dose-response curves for each. The correlation between animal carcinogenicity and bacterial mutagenicity was excellent for 10 of the 14 compounds. The other four compounds (all nitroso-compounds) were more potent as carcinogens than as mutagens.

A spirited exchange of views resulted from the suggestion that quantitative relationships exist between mutagenicity in the Ames test and carcinogenicity in animal tests. Ashby and Styles (18) challenged the idea that such relationships were common, and Ames and Hooper (12) responded that they were.

The International Program for the Evaluation of Short-Term Tests for Carcinogenicity (188) distributed 42 chemicals to each of 12 laboratories for testing in the Ames system: To eliminate bias, none of the laboratories knew the identity of the chemicals. There was excellent agreement among test results obtained in different laboratories and about 80 percent of the carcinogens were scored as mutagens and about 80 percent of the noncarcinogens were scored as nonmutagens. These numbers compare well with those in the literature that describe results from experiments in which the investigators knew before the mutagenicity test was run that the chemicals were or were not carcinogenic. Although the 80-percent is lower than the 90-percent accuracy sometimes reported, the program included a number of chemicals that are known to present difficulties for the Ames test. In a qualitative sense, the test performed very well, but mutagenic potency did not correlate with carcinogenic potency. In other words, the results from this program do not support the idea that there is a quantitative relationship between Ames test results and carcinogenicity in animals. Similar results showing good qualitative and poor quantitative agreements between mutagenicity and carcinogenicity were reported by Bartsch et al. (22).

Meselson and Russell (235) reported that sufficient quantitative data were available for two human carcinogens, aflatoxin B and cigarette smoke, to allow comparison of mutagenic potency to carcinogenic potency in humans. Correlation between carcinogenicity in humans and mutagenicity was good for the two compounds, and the Meselson and Russell paper raised the possibility that human cancer risks might be predicted from mutagenicity data. Acceptance of such a procedure is far away and will depend on much more data being available to support the proposed quantitative relationships.

Clearly, controversies now exist about the value of extrapolations made from short-term tests. It seems reasonable that, as use of short-term tests increases, such projections are going to be made, but some initial optimism about the value of quantitative extrapolation from short-term tests to carcinogenicity is apparently fading.

CARCINOGENIC ACTIVITY INDICATORS

The NRC Pesticide Committee (267) recommends calculating potency expressions, "Carcinogenic Activity Indicators" (CAI), for tested chemicals. For each point of a dose response curve (fig. 21), the number of chemical molecules ingested divided by the animal body weight can be related to the excess percentage of tumor-bearing animals in the exposed population.

$$CAI = \frac{\text{excess percentage of subjects in which tumors are observed}}{\text{lifetime dose (molecules/kg of body weight)}} = \frac{\text{tumor incidence}}{\text{dose}}$$

CAIs do not have to be based on total tumors, for instance, site specific tumors may be counted, the analysis may be limited to one sex, only malignant tumors may be counted, or other alterations can be made as wanted. In practice, the number of molecules of different substances, S1, S2, and S3 required to induce the same percentage of excess tumors can be compared to determine which is the most potent carcinogen. CAIs will probably be different for each point on a dose-response curve because the points seldom fall in a straight line, but comparisons can be made at comparable doses.

Using information about exposure levels for human populations, the number of molecules that compare to human exposures can be calculated. Linear extrapolation is then to be used to estimate the animal response at human exposure level. This method is especially appropriate for comparing chemicals with similar uses, and if applied, would assure that the most and least risky ones based on animal data are identified.

The procedure does not make predictions of human cancer risks from animal data and avoids the problems associated with biologic extrapolation. The NRC committee (267) urges that only epidemiologic data be used to estimate human risk; it restricts the use of animal data to making comparisons of carcinogenicity in animals. (Such an approach is especially attractive when deciding about regulating pesticides. Substitutes are often available and CAIs offer a method to decide on the less or least risky one. This suggestion corresponds to the second possible use of extrapolation discussed in *Quantitative Effects of Selecting a Model* above.)

POTENCY

Ames et al. (14) have analyzed more than 1,500 bioassays carried out on some 600 chemicals. For each experiment, they have calculated a potency index, TD_{50}, which is calculated as the total dose of substance necessary to produce tumors in 50 percent of the animals. They expect to compare potency:

1. among multiple tests run on the same substance in the same strain and species;
2. between male and female animals;
3. between different strains of the same animal;
4. between different sites in different animals; and
5. between rodent tests and 26 tests that have been carried out in monkeys.

The results of this massive project is expected to provide much information about biologic extrapolation from species to species and about potencies.

Ames et al. (14) mention that preliminary results show that there is usually less than a tenfold variation in potencies among rodents. This level of agreement was also found by Crouch and Wilson (72) for most of 70 chemicals tested in both rats and mice by NCI. Crouch and Wilson included tumors which were not present at "statistically significant" levels in their analyses. Therefore, some chemicals judged positive in only one species by NCI (146) have potencies that agree within a factor of 10 between rats and mice although one is statistically significant and

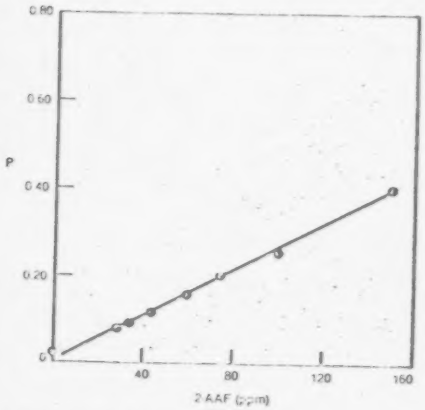
the other is not. Results showing a substance is much more potent in one species than in another will suggest that metabolism of the chemical differs from species to species. This information will also be important in efforts to improve extrapolation methods.

THE ED_{01} EXPERIMENT AND EXTRAPOLATION MODELS

The National Center for Toxicological Research, a joint FDA/EPA laboratory, tested the known bladder and liver carcinogen 2-acetylaminofluorene (2-AAF) in approximately 24,000 female mice. This experiment was designed to study dose responses down to a 1-percent tumor incidence, i.e., the effective dose for a 1-percent (0.01) response (ED_{01}).

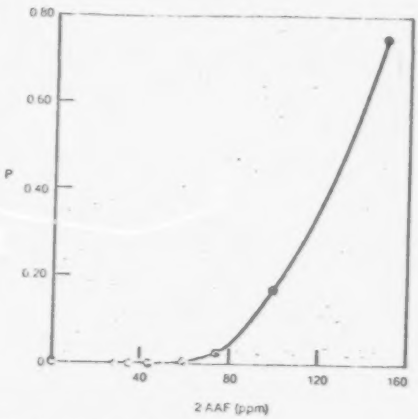
Figures 22 and 23 show the results of postmortem examination for liver and bladder tumors in animals exposed to 2-AAF for between 21.5 and 28.5 months. The curve that describes the liver tumors (fig. 22) shows no threshold and increases almost proportionally to dose. The curve that describes the bladder tumors (fig. 23) gives an impression of a "threshold" dose below 60 ppm of 2-AAF. Gaylor (136)

Figure 22.—Proportion (P) of Mice With Liver Tumors v. Dose (21.5 to 28.5 months)



SOURCE: Littlefield, et al. (213).

Figure 23.—Proportion (P) of Mice With Bladder Tumors v. Dose (21.5 to 28.5 months)

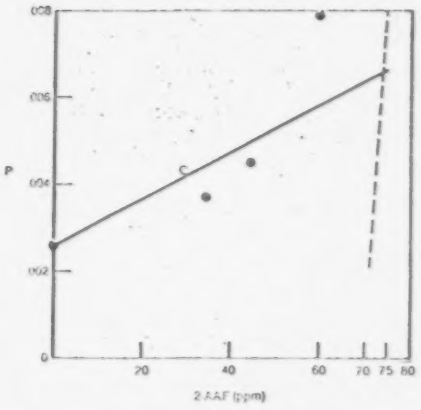


SOURCE: Littlefield, et al. (213).

ascribes the apparent threshold to a lack of resolution of the graph for low tumor rates. He replotted these same data on an enlarged scale (figure 24) to show that the number of bladder tumors increases with dose even at lower doses. This diagram supports the idea that there was no threshold. However, there is a dramatic change in slope of the line between 60 and 75 ppm, and the efficiency of 2-AAF in causing tumors increases greatly at doses above 60 ppm (fig. 24).

Carlborg (50) has also analyzed the data from ED_{01}. He does not argue that the bladder cancer data show a threshold, but he does contend that neither the bladder nor the liver data fit a one-hit (linear) model. In addition to trying to fit a one-hit model to the data, he also tried the

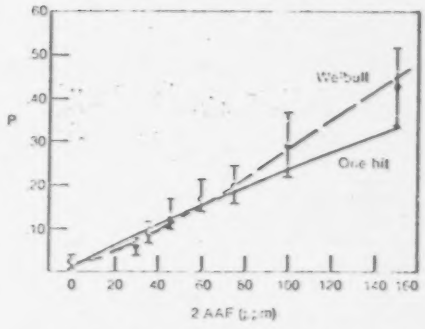
Figure 24.—Proportion (P) of Mice With Bladder Tumors v. Dose (21.5 to 28.5 months)



NOTE: The vertical scale has been expanded 100 times compared to figure 23.
—— line fitted to data points between 0 and 60 ppm
- - - - slope of line between 60 and 75 ppm determined from figure 23

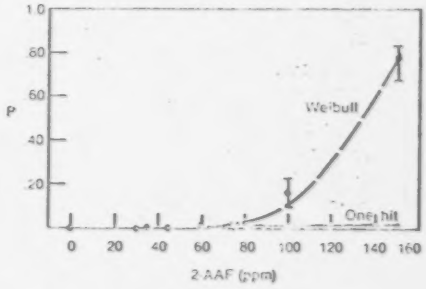
SOURCE: Gaylor (136) and Office of Technology Assessment.

Figure 25.—Proportion (P) of Mice With Liver Tumors v. Dose (24 months)



SOURCE: Carlborg (50).

Figure 26.—Proportion (P) of Mice With Bladder Tumors v. Dose (24 months)



SOURCE: Carlborg (50).

Weibull model, a "generalization of the one-hit model." Figures 25 and 26 represent his analysis of the two sets of data, and the "best-fitting one-hit and Weibull models" are plotted in both figures. It can be seen that the Weibull model provides a better fit, especially with the bladder tumor data. Carlborg (50) also states that the one-hit model fits well with only the three lowest dose points from the liver tumor data.

The Weibull model produces a different slope for the line to be drawn from 30 to 0 ppm. Carlborg calculates that a 0.000045 ppm dose of 2-AAF is necessary to produce a one in a million risk of liver cancer using the one-hit model. Using the Weibull model, the calculated dose for a one in a million risk is 100 times higher, 0.0045 ppm. In other words, use of the Weibull model would allow exposures 100 times higher than the linear model if there were agreement that a one in a million risk were acceptable.

Despite the large number of data points from ED_{01}, Gaylor (136) argues that a "best" model cannot be chosen on the basis of fit with the data and that the Weibull model cannot be singled out above all others. Furthermore, he says that several models fit the observed data about equally well, and that they predict very different levels of risk at doses between 0 and 30 ppm 2-AAF (see discussion of different models in 35,49,51,123,170).

Obviously, animal data can be best used quantitatively to estimate potential risks within the same animal species under test conditions. These estimates cannot be used directly to estimate human risks. Other "biologic" assumptions are necessary to extrapolate from animal data to estimates of human risk.

BIOLOGIC EXTRAPOLATION FROM ANIMAL TESTS

Bioassay guidelines call for testing in two species. Qualitative judgments are based on whether a tested substance causes tumors in both, only one, or neither species. Sometimes, a substance is reported positive (causes tumors) in only one species and negative in another. The frequency with which this problem is encountered can be estimated from Griesemer and Cueto's (146) discussion of the results of the NCI bioassay program (see app. A). Of the 98 chemicals for which "very strong" or "sufficient" evidence of carcinogenicity was found in either rats, mice, or both, 54 were positive in only one species. An analysis of test results from 250 substances (300) found 38 percent were carcinogenic in neither rats nor mice, 15 percent were carcinogenic in either the rat or the mouse but not both, and 44 percent were carcinogenic in both. Crouch and Wilson (72) and Ames et al. (14) tend to dismiss these discordant results between rats and mice because tests analyzed by their methods, which consider experimental error and test sensitivity, are in agreement much more often.

In cases in which there are apparent species differences in sensitivity, the positive result is generally accepted as more important. The Office of Science and Technology Policy (281), IRLG (180), the Occupational Safety and Health Administration (279), and American Federation of Labor/Congress of Industrial Organizations (7) all present arguments for following this course. AIHC (8) and Purchase (300) present arguments against deciding that the more sensitive animal is predictive for human response. The disagreement continues, but in Federal programs, extrapolation is based on results from the more sensitive species.

Accepting that experimental animals provide appropriate data for extrapolation to estimates of human risk, a decision has to be made about how to adjust the dose measured in the bioassay to the dose experienced by humans. A mouse or rat, of course, is much smaller than a human, and the dose necessary to cause a carcinogenic response is less than that required in humans. Three "scaling factors" are in general use to make allowance for the different sizes and rates of metabolism between experimental animals and humans. The three are listed below in order from least conservative, that is the one that predicts the lowest human risk, to the most conservative. The fourth scaling factor is less often used, but it is included because it was used for the estimates reported in table 34. For rats and mice, the most commonly used laboratory animals, the relationship between scaling factors and estimated risk in man for the same doses are shown in table 33.

1. Exposures may be adjusted on the basis of relative body weights, milligram of agent/kilogram of body weight/day (mg/kg/day), for animals and humans. This method is most generally used by toxicologists.
2. In cases where the experimental dose is measured as parts per million in food, air, or water and human exposure is through ingestion, the dose of the chemical is expressed as parts per million. This method is generally used by FDA and in some cases by EPA.
3. Exposure may be adjusted on the basis of the relative surface areas of the test animal and humans: milligram of agent/surface area/day, for animals and humans. It is generally expressed as milligram of substance/square meter of surface area/day or mg/m²/day. EPA uses this scaling factor.

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Table 33.—Relative Human Risk Depending on How Dose Rate is Scaled From Experimental Animals to Humans

	Risk projected for humans when an identical dose is scaled by different factors			
	Milligram	Parts per million	Milligram	Milligram
Experimental animal	Kilogram body weight/day	In diet	m^2 body area	Kilogram body weight/lifetime
Mouse	1	6	14	40
Rat	1	3	6	35

SOURCE: Office of Technology Assessment.

4. Exposures may be adjusted on the basis of relative body weight over lifetime, milligrams of agent/kilogram of body weight/lifetime (mg/kg/lifetime).

As can be seen from table 33, the choice of scaling factor can make a difference of up to fortyfold in estimating human risks. The mg/kg/day scaling factor was arbitarily set equal to 1.0. Use of the mg/m^2/day factor (for instance) projects that humans would have 14 times the risk of a mouse for equivalent doses measured in mg/kg/day. The information given in table 33 allows a comparison to be made among the scaling factors. However, it is important to remember that great uncertainties surround biologic extrapolation because of possible differences between laboratory animals and man, and no great assurance is attached to any number in table 33.

COMPARING MEASURED HUMAN CANCER INCIDENCE AND MORTALITY TO ESTIMATES MADE USING EXTRAPOLATION

The more troubling and more fundamental problem with biologic extrapolation concerns questions about how closely the test animal resembles humans. This problem is partially related to differences in the greater genetic complexity of human populations. Populations of test animals are highly inbred and are almost genetically identical. Populations of humans are outbred and include greatly differing genotypes. There is no way to deal with the problem of humans that may differ in sensitivities because there is seldom, if ever, a way to associate sensitivities with individuals. The other problem concerns differences in metabolism between test animals and humans. Few are well understood, and many may be unidentified.

Laying these problems aside, a few efforts have been made to compare human cancer incidence or mortality to the levels of incidence or mortality extrapolated from animal studies. The number of such attempts is limited by the few cases for which data are available both from experimental animals and from humans. The Consultative Panel on Health Hazards of Chemical Pesticides of the National Research Council's Study of Pest Control (262), identified six chemicals for which such comparisons could be made. Comparisons were made on the basis of lifetime dosage (expressed as milligram chemical/kilogram body weight/lifetime) in animals and in humans. Table 34 shows those findings. It can be seen that for three chemicals the incidence of human tumors was essentially that predicted from animal studies, and for the other three, extrapolation from animal data overestimated human risk as measured by epidemiology. Crouch and Wilson (72) have made similar comparisons for 13 chemicals (including the 6 in table 34). They reported good agreement between predicted and observed human tumors rates, using a linear nonthreshold extrapolation model. Crouch and Wilson (72) also calculated "scaling factors" from their experiments and concluded that humans are twice as sensitive as mice and between one-third and three times as sensitive as rats to the same dose expressed as mg/kg/day. These values differ

Table 34.—Comparison of Tumor Rates in Laboratory Test Animals and Humans Following Lifetime Exposures to Comparable Amounts of Each of Six Agents[1]
(comparison based on mg agent/kg bodyweight/lifetime)

Chemical	Test animal	Animal tumor site(s)	Human tumor site	Relative tumor rate[a]
Benzidine	Mouse Rat	Liver Bladder	Bladder	ca. 1
Cigarette smoking	Mouse Hamster	Lung Larynx	Lung	ca. 1
N,N-bis(2-chloroethyl) 2 naphtylamine	Mouse	Lung	Bladder	ca. 1
Aflatoxin B_1	Mouse Rat	Liver Liver	Liver	ca. 10
Diethylstilbestrol (DES)	Mouse	Mammary	Daughters' reproductive tract	ca. 50
	Mouse	Cervix and vagina		
Vinyl chloride	Mouse Mouse Rat Rat	Lung Mammary Kidney Liver	Liver	ca. 500

[a] Relative tumor rate = $\frac{\text{tumor incidence predicted from most sensitive animal species}}{\text{tumor incidence observed in humans}}$

SOURCE: Adapted from National Research Council (262).

from unity by a factor of 3 or less which is assumed for doses scaled on the basis of mg/kg/day (see table 33).

A decision about whether the reasonably good agreement between extrapolated values and observations (72,262) are of significance, and whether or not these findings mean extrapolation is accurate enough for making quantitative decisions about human risks depends on the observer. The NRC Committee (262) concluded that:

> Although there are major uncertainties in extrapolating the results of animal tests to man, this is usually the only available method . . . Despite the uncertainties, enough is known to indicate what dependencies on dose and time may operate and to provide rough predictions of induced cancer rates in human populations.

Regulating Pesticides, a report prepared by the National Academy of Science's Committee on Prototype Explicit Analyses for Pesticides (267), says that seven previous National Research Council reports have recommended extrapolating from animal data to projected human risk. The Committee (267) took a different position and recommended that only epidemiologic data be used to estimate human risk:

> OPP [Office of Pesticide Programs, EPA] should abandon its attempts to produce numerical estimates of the effects of the use of pesticides on human mortality and morbidity except when reliable human epidemiological data are available. In the usual case, in which major reliance has to be placed on the results of bioassays, those results should be used to construct indicators of the relative pathological activity of the pesticide under review in comparison with other pesticides and compounds.

Documented differences between the metabolism of a chemical in test animals and in humans would be very useful in any attempt at biologic extrapolation. Poor understanding of comparative biochemistry hampers research in the basic biology of cancer. As research con-

tinues, knowledge of metabolic differences between animals and humans may provide clearer direction, but such information will always be limited by strong constraints on studying metabolism of carcinogens in humans.

SUMMARY

Animal tests or epidemiologic studies yield data that relate cancer (or tumor) incidence to exposure levels (dosage) of the substance under study. The accuracy of the relation between exposure and incidence is always limited. Practical restraints on the number of animals that can be tested means that the data are always subject to significant experimental error; it also means that only relatively high incidences almost always greater than 10 percent, can be measured in the experiments. Epidemiologic studies may be limited by small numbers of people available for study, or by unknown or uncertain exposure levels. In all cases, deficiencies in experimental design and execution may further limit the accuracy of relating incidence to dose.

Quantitative extrapolation begins with the experimentally determined relationship between incidence and exposure and may use one of several methods to derive an estimate of incidence at exposure levels likely to be encountered in the environment. When animal data are used for extrapolation one of four scaling factors can be used to extrapolate from animal results to expected human response. The scaling factors vary some fortyfold in the risk they project for humans, and agreement has not been reached about which one is most appropriate.

There is also no agreement about which mathematical models best extrapolate from the exposure levels measured in studies to those encountered in the environment. Linear models, which assume that incidence is proportional to exposure at low-exposure levels, are used by Federal agencies. Some other organizations favor nonlinear models in which estimates of incidence decrease faster than dose decreases. A special feature of some models is the incorporation of a threshold, a low, but nonzero exposure level at which the estimated incidence is zero. Nonthreshold models, which are used by Federal agencies, associate some positive estimate of incidence with all doses above zero.

Suggestions are frequently made that careful inspection of available data and testing various extrapolation models against them will allow selection of the best model. Unfortunately data are not sufficient to make such judgments. Another method to decide which model is appropriate is to make projections from animal data and compare these to observed incidence in humans. The cases where human data are available to make comparisons are few, but the conceptually simple, linear, nonthreshold model is reported to estimate human incidence reasonably well.

The increasing importance of short-term tests has led to efforts to extrapolate from them to estimates of carcinogenic risks in humans or animals. Qualitatively short-term tests perform well in predicting whether a substance will be carcinogenic or noncarcinogenic in an animal test. Quantitative agreement between mutagenic potency in short-term tests and carcinogenic potency in animal tests for carcinogenicity is not nearly so good.

APPENDIX F

IARC MONOGRAPH 9

NOTE TO THE READER

The term 'carcinogenic risk' in the IARC Monograph series is taken to mean the probability that exposure to the chemical will lead to cancer in humans.

Inclusion of a chemical in the monographs does not imply that it is a carcinogen, only that published data have been examined. Equally, the fact that a chemical has not yet been evaluated in a monograph does not mean that it is not carcinogenic.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of a chemical for humans is encouraged to make this information available to the Division of Chemical and Biological Carcinogenesis, International Agency for Research on Cancer, Lyon, France, in order that the chemical may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the monographs as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Division of Chemical and Biological Carcinogenesis, so that corrections can be reported in future volumes.

Information compiled from the first 24 volumes of the *IARC Monographs*(17-19) shows that of the 37 chemicals, groups of chemicals or manufacturing processes now generally accepted to cause or probably to cause cancer in humans, all but possibly two (arsenic and benzene) of those which have been tested appropriately produce cancer in at least one animal species. For several of the chemicals that are carcinogenic for humans (aflatoxins, 4-aminobiphenyl, diethylstilboestrol, melphalan, mustard gas and vinyl chloride), evidence of carcinogenicity in experimental animals preceded evidence obtained from epidemiological studies or case reports.

In general, the evidence that a chemical produces tumours in experimental animals is of two degrees: (a) *sufficient evidence* of carcinogenicity is provided by the production of malignant tumours; and (b) *limited evidence* of carcinogenicity reflects qualitative and/or quantitative limitations of the experimental results.

For many of the chemicals evaluated in the first 24 volumes of the *IARC Monographs* for which there is *sufficient evidence* of carcinogenicity in animals, data relating to carcinogenicity for humans are either insufficient or nonexistent. In the absence of adequate data on humans, it is reasonable, for practical purposes, to regard such chemicals as if they presented a carcinogenic risk to humans.

Sufficient evidence of carcinogenicity is provided by experimental studies that show an increased incidence of malignant tumours: (i) in multiple species or strains, and/or (ii) in multiple experiments (routes and/or doses), and/or (iii) to an unusual degree (with regard to incidence, site, type and/or precocity of onset). Additional evidence may be provided by data concerning dose-response, mutagenicity or structure.

In the present state of knowledge, it would be difficult to define a predictable relationship between the dose (mg/kg bw/day) of a particular chemical required to produce cancer in test animals and the dose which would produce a similar incidence of cancer in humans. The available data suggest, however, that such a relationship may exist(20,21), at least for certain classes of carcinogenic chemicals. Data that provide *sufficient evidence* of carcinogenicity in test animals may therefore be used in an approximate quantitative evaluation of the human risk at some given exposure level, provided that the nature of the chemical concerned and the physiological, pharmacological and toxicological differences between the test animals and humans are taken into account. However, no acceptable methods are currently available for quantifying the possible errors in such a procedure, whether it is used to generalize between species or to extrapolate from high to low doses. The methodology for such quantitative extrapolation to humans requires further development.

Evidence for the carcinogenicity of some chemicals in experimental animals may be *limited* for two reasons. Firstly, experimental data may be restricted to such a point that it is not possible to determine a causal relationship between administration of a chemical and the development of a particular lesion in the animals. Secondly, there are certain neoplasms, including lung tumours and hepatomas in mice, which have been considered of lesser significance than neoplasms occurring at other sites for the purpose of evaluating the carcinogenicity of chemicals. Such tumours occur spontaneously in high incidence in these animals, and their malignancy is often difficult to establish. An evaluation of the significance of these tumours following administration of a chemical is the responsibility of particular Working Groups preparing individual monographs, and it has not been possible to set down rigid guidelines; the relevance of these tumours must be determined by considerations which include experimental design and completeness of reporting.

Some chemicals for which there is *limited evidence* of carcinogenicity in animals have also been studied in humans with, in general, inconclusive results. While such chemicals may indeed be carcinogenic to humans, more experimental and epidemiological investigation is required.

Hence *'sufficient evidence'* of carcinogenicity and *'limited evidence'* of carcinogenicity do not indicate categories of chemicals: the inherent definitions of those terms indicate varying degrees of experimental evidence, which may change if and when new data on the chemicals become available. The main drawback to any rigid classification of chemicals with regard to their carcinogenic capacity is the as yet incomplete knowledge of the mechanism(s) of carcinogenesis.

In recent years, several short-term tests for the detection of potential carcinogens have been developed. When only inadequate experimental data are available, positive results in validated short-term tests (see p. 23) are an indication that the compound is a potential carcinogen and that it should be tested in animals for an assessment of its carcinogenicity. Negative results from short-term tests cannot be considered sufficient evidence to rule out carcinogenicity. Whether short-term tests will eventually be as reliable as long-term tests in predicting carcinogenicity in humans will depend on further demonstrations of consistency with long-term experiments and with data from humans.

ADDITIONAL VIEWS OF HON. LARRY WINN, JR., HON. ROBERT S. WALKER, AND HON. MANUEL LUJAN, JR.

Review of the Scientific Basis of the EPA's Carcinogenic Risk Assessment of Formaldehyde

The central question in the minds of many Members of Congress on the issue of formaldehyde was not whether the chemical should be regulated, but, whether there was sufficient evidence of potential human carcinogenicity to support accelerated regulation under the "fast-track" provisions of section 4(f) of the Toxic Substances Control Act. This concern is correctly articulated in the draft report written by the majority staff as it appears on page 6, "The public controversy over EPA's decision focused on the question of whether formaldehyde presented an 'unreasonable' cancer risk to humans, and, therefore, whether EPA should have acted expeditiously—as the CPSC had done—to control exposure to formaldehyde.

During the course of the hearing it was obvious to some of the participants that formaldehyde did present a possible risk. The evidence seemed to indicate that long exposures to sufficiently high concentrations of the chemical would eventually lead to cancers in laboratory animals. However, the levels which resulted in cancers in these animals were considerably higher than any which would be tolerated by humans for even short intervals.

As the majority takes pains to point out in the introduction, formaldehyde is used in hundreds of products in daily use by the average consumer, and has been in general use for nearly 100 years. Section 4(f) requires that chemicals be designated for priority regulatory action when . . . "there may be a reasonable basis to conclude that a chemical substance or mixture presents, or will present, significant risk of serious or widespread harm to human beings from cancer, gene mutations, or birth defects . . ."

The crucial question facing the regulators at EPA was whether formaldehyde presented such a serious risk as to require priority regulatory activity. We would submit that this is a question which must be viewed with some care in the case of a chemical in such widespread use as formaldehyde.

There is considerable evidence that the vast majority of cancers are multifactorial, that is to say that they are caused by the additive effects of a number of causes including environmental factors in the home and work place, individual life style and genetic factors. The cause and effect relationship between some cancers—such as smoking and lung cancers—is impossible to ignore even though the government does not regulate the use of tobacco. In other cases, and we would submit that formaldehyde is one of these, the evidence is nowhere near as overwhelming as the link between tobacco and lung cancer. In these cases

the epidemiological evidence of human carcinogenicity is inconclusive, and regulatory decisions in these cases should be approached with great care.

In the specific case of formaldehyde there was conclusive evidence that the chemical was, in fact, carcinogenic in animals. From that conclusion it may be argued that formaldehyde, as a proven animal carcinogen, should be treated as a potential human carcinogen. We do not believe that EPA rejected that potential. It appears to us that the EPA decision did not reject the possibility that formaldehyde might be a human carcinogen, but rather, rejected formaldehyde as a chemical for priority regulation under the provisions of section 4(f) on the basis that the available scientific information did not support priority regulation.

The majority members of the Committee make much of the fact that the United States Consumer Product Safety Commission, using scientific data which was virtually identical to that available to the Environmental Protection Agency concerning formaldehyde, elected to issue a rule banning the use of urea-formaldehyde foam in home insulation, and in schools on April 2, 1982. This final rule was issued at the conclusion of a 6-year investigation and rulemaking effort. The Consumer Product Safety Commission found that UFFI presented an unreasonable risk from irritation and cancer and that no feasible product standard exists that would adequately protect the public from the hazards.

Four petitions for review of the CPSC rule were quickly filed in the United States Court for Appeals for the District of Columbia Circuit. In an opinion dated July 2, 1982, the U.S. Court of Appeals for the Fifth Circuit was determined to be proper venue and all petitions for review were consolidated there.

On April 7, 1983, the U.S. Court of Appeals for the Fifth Circuit, in a strongly worded unanimous opinion, which is included in its entirety as part of these views, ruled that the CPSC record developed before the Commission "did not contain the substantial evidence necessary to support the Commission's ban on the use of urea-formaldehyde foam insulation . . ." (*Gulf South Insulation, et al Petitioners* v. *United States Consumer Product Safety Commission*, Respondent, — F2d —, (5th Cir. April 7, 1983).

We realize that the issues before the fifth circuit were not exactly the issues which the majority attempted to establish in the course of our hearings. However, we believe that in this instance there are several valuable lessons to be yearned from the findings of the Circuit Court of Appeals.

The first lesson is that the Court was viewing the entire record of the proceedings and had access to not only the CPSC record, but also had benefits of the views of petitioners who were opposed to the Commission ban both on grounds that it was not sufficiently strong, and that it should have been extended to all structures in the case of Public Citizen (No. 82–4311), and that the ban was not supported by the evidence in the case of industry petitioners. In viewing the entire record the Court was able to weigh the various viewpoints, consider all of the available evidence, and reach a determination. This record contains 6 years accumulation of evidence and thousands of pages of materials, as versus no more than a few hundred pages of materials

from our witnesses. This record is far more likely to contain a full, and well-rounded examination of the subject, rather than the possibly one-dimensional view developed in a single congressional hearing. And this record must contain more, and better data upon which to make scientific and regulatory judgments than the record of a short congressional oversight hearing.

The second lesson is that in the area of environmental regulation there is still considerable room for disagreement among highly qualified scientists and regulators. The CPSC had conducted a lengthy and exhaustive investigation of the potential risks which might be associated with human exposure to formaldehyde. They accepted a number of assumptions which they considered reasonable in the course of reaching their decision to ban urea formaldehyde foam insulation because it represented an "unreasonable risk." However, the Fifth Circuit Court of Appeals specifically found that the studies used in making that determination to ban the product "were inadequate to serve as a data base," that the use of the Chemical Institute study by the CPSC was invalid since "to make precise estimates, precise data are required," and that the predictions made by the CPSC risk assessment model were no better than the data base, and that the data base was inadequate. The Court therefore concluded, "The result is that the Commission's finding that UFFI poses an unreasonable risk of cancer is not supported by substantial evidence on the record as a whole."

We are in agreement with the Court in its conclusion, "We are not unmindful that regulating in the face of scientific uncertainty within ever tightening budgetary constraints presents the Commission with a difficult task." We fully concur with that sentiment. And we also concur with the Court that there is a heavy duty to take a "harder look" to determine whether rules and regulations adopted by CPSC, EPA and other agencies are supported by substantial evidence.

In the case of formaldehyde the courts have found that the CPSC was wrong to regulate and that the evidence was not there to support the action of the Commission. In the case of EPA the majority attempts to claim that they were wrong not to move to regulate formaldehyde based on essentially the same evidence as a priority chemical under section 4(f) of the Toxic Substances Control Act. We submit that the same evidence which led the court to conclude that CPSC acted in error supports the decision reached at EPA.

MANUEL LUJAN, Jr.
ROBERT S. WALKER.
LARRY WINN, Jr.

MINORITY VIEWS

Review on the Environmental Protection Agency's Carcinogenic Risk Assessment on Formaldehyde

subcommittee on investigations and oversight

The minority concurs with the subcommittee on the importance of proper environmental safeguards in the case of potential chemical carcinogens.

We take issue, however, with the timing of the report's release and with the tone expressed throughout. The hearing upon which the report is based was held on 20 May 1982, during the 97th Congress. Traditionally, and we think for good reason, subcommittee reports are issued in the same Congress in which the original hearing was held. This policy is a wise one, and is especially important in protecting the rights of the minority. To illustrate the problem, we would like to review our current situation on this report. First, none of the minority members who served on the subcommittee in the 97th Congress still serve on the subcommittee in the current Congress. In addition, the minority counsel serving the minority members in the 97th Congress is no longer with the subcommittee. The result places the minority members currently on the subcommittee in the untenable position of approving a controversial report without having the benefit of participating in the hearing or benefiting from the advice of the minority staff serving the subcommittee at that time.

We are being asked, subsequently, to support the issuance of a report in an informational and policy vacuum. We therefore have no basis upon which to judge the merits of the report's recommendations. We strongly disagree with this process, and feel it is indecorous for this subcommittee.

In addition, the minority disagrees with the tone in much of the report. In issues involving controversial issues where the scientific community is not in agreement (as in this case), we feel the impartiality of the subcommittee is vitally important. The respect of our congressional colleagues, the scientific community, and the public is at stake here; rash, subjective statements and conclusions are not appropriate.

Again, the minority agrees that the regulations governing the public's exposure to potential carcinogens are of the utmost importance. We support the subcommittee's oversight activities in this area; it is unfortunate and regrettable that the report takes on such a polemical tone.

Larry Winn, Jr.
Joe Skeen.
Claudine Schneider.
Alfred A. McCandless.